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The American Heart Journal

VOL. 20 OCTOBER, 1940 NO. 4

Original Communications

A MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM IN UNGULATES, DOG, AND MAN

PART I: THE SINOATRIAL NODE

DANIEL J. GLOMSET, M.D., AND ANNA T. A. GLOMSET, B.S.
DES MOINES, IOWA

IN 1907 Keith and Flack[1] described a neuromuscular node which they had found in the right atrial myocardium near the mouth of the superior vena cava. They stated that the structure of this tissue was similar to that of the auriculoventricular node, described by Tawara,[2] and that the heart beat originated in this node. Their statements were generally accepted, and used to supply the "missing link" in the chain of morphologic evidence in favor of the myogenic theory of the origin and transmission of the cardiac impulse. By ingenious electrocardiographic experiments, Lewis,[3] in 1913, showed that the heart beat originated in this region, and that the impulse spread thence to the rest of the heart. Thus, the node of Keith and Flack was established as the "primum movens et ultimum moriens" of the heart; and the node, together with the Purkinje system, became the morphologic basis upon which subsequent knowledge of conduction developed.

A study of the available literature on the sinoatrial node, however, brings to light many conflicting observations. Most experiments on ablation of the sinoatrial node fail to show convincingly that the node is the pacemaker of the heart (Flack,[4] Jaeger,[5] Magnus-Alsleben,[6] Moorhouse,[7] Brandenburg and Hoffmann,[8] Eyster and Meek,[9] and Borman[10]), and there is no unanimity of opinion as to the location, size, and structure of the node. The discoverers of the node say that it lies in the sulcus terminalis. In the human heart its muscle fibers are imbedded in dense fibrous tissue around an artery (or a circle of arteries) which is usually found on the caval side of the sulcus. This means that most of the node must lie on the caval side. According to Koch[11] the node is spindle-shaped, and the head of the spindle lies in the upper third of the sulcus, a millimeter or so below the angle made by the cava and

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the atrial wall. It tapers as it runs downward, and ends left of the middle of the inferior vena cava at its junction with the auricle. A slender fasciculus runs upward from the head, either over the cava or over the atrium. It is evident that Koch found the node on the atrial side of the sulcus. Walmsley[12] states that the node is spindle-shaped, and measures 20, by 3, by 1 mm. It gives off fine processes which pass over the superior vena cava and into the atrial musculature. In his illustration, the head of the spindle lies at the top of the sulcus. Bruni[13] modeled the node from serial sections of the hearts of cattle. His model of the node is composed of an upper "head," and a lower, "horseshoe-shaped" portion. The "head" lies across the upper part of the sulcus, and hornlike processes run from it, one on the cava, and the other toward the interatrial septum. The "horseshoe" portion straddles the superior vena cava at its entrance to the auricle. One end of the "horseshoe" runs anteriorly, and the other posteriorly, around the cava on the atrial side of the sulcus. In sheep, Bruni found only the "horseshoe" part. Blair and Davies[14] found only the "horseshoe" part in man and in cattle. Lewis[3] pictures the node, in the dog, on the caval side of the sulcus, head up. Shaner,[15] who also studied the node in cattle, found its anlage in the musculature of the superior vena cava above the sulcus, and states that it descends to the groove at birth. In the adult animal the node lies across the cava. Its upper part is separated from the atrium by connective tissue, but the lower portion is directly continuous with the atrial musculature. Mettam[16] found that, in the horse, the node is an ill-defined, whitish structure. Its long axis runs parallel to the sulcus, and it is 3 cm. long by 5 mm. broad.

Cohn,[17] Blair and Davies,[14] and others have found that the nodal tissue, in man, extends from epicardium to endocardium. In rabbits, Koch pictures it involving approximately half of the myocardium; the same is true in hogs, according to Lewis. Most of the investigators agree with the discoverers that the nodal muscle fibers form a network around, or lateral to, the artery (or arteries) in the sulcus. The tortuosity of the muscle fasciculi accounts, they assert, for the fact that such a network is not apparent histologically. Koch was not impressed by the network formation within the node. Blair and Davies state that most of the fibers run vertically, and that the sinoauricular node does not resemble the node of Tawara. According to most observers, the differentiating features of the special muscle elements are the following:

1. The fibers are a trifle more slender than ordinary atrial fibers.
2. The fibers are faintly striated (Yater,[18] Burian,[19] Blair and Davies,[14] and others). Burian, and Blair and Davies also described a clear perinuclear zone comparable to that found in Purkinje fibers.
3. The nodal fibers are tortuous.
4. Branching is frequent.

5. The nuclei are round or oval, and, occasionally, multiple.

6. The nodal elements are directly continuous with the atrial and the caval musculature.

7. Keith and Flack found ganglion cells and nerve trunks within the substance of the node. Subsequent observers, however, located these around the periphery of the node.

8. Several observers have noted that the muscle fibers of the node are directly continuous with the musculature of the nodal artery.

In order to "illumine that which to us was dark," we undertook a gross and microscopic examination of the sulcus region in thirteen human, six canine, eight bovine, seven ovine, three porcine, and two equine hearts. The hearts used for gross dissection were fixed in Kaiserling I. The blocks used for microscopic study were fixed in Bouin's solution, or in a 10 per cent solution of formalin. The sections were stained routinely with iron hematoxylin, and at times counterstained by van Gieson's method. Sections were cut longitudinally at three levels, viz., the atrial side, the bottom, and the caval side of the sulcus terminalis, and, transversely, from the upper, middle, and lower parts of the sulcus. For comparative purposes, the regions around the pulmonary veins, the inferior vena cava, and the pulmonary artery, as well as various places in the right and the left atrioventricular groove, were studied grossly and microscopically.

GROSS ANATOMY OF THE NODAL REGION

This part of our investigation was undertaken because Walmsley states that the node can be exposed by gross dissection, and can be seen, when the epicardium is removed, as a yellowish body lying deep in the upper part of the sulcus. When we carefully removed the pericardium and the loose areolar tissue from the atrium and the veins, the arrangement of the regional muscles was revealed. The most striking feature which was observed during the removal of the epicardium was the large number of nerve trunks running over the great veins and over every part of the atria. A second outstanding feature was the extension of the atrial musculature from one-fourth of an inch to 2 inches up the walls of the great veins.

Perhaps the muscular arrangement in the region of the superior vena cava can be best described by beginning with Bachman's bundle.* This is a stout band of muscle which extends transversely behind the aorta, between the anterior portions of the bases of the auricular appendages. At the right end of this bundle the fibers spread out fanlike, forming a continuous sheet which extends over the right atrium posteriorly to the left of the vena cava, around the cava itself, over the edges and the bottom of the sulcus terminalis, and over the right auricular appendage. Thus, the cava lies in the buttonhole-like opening of this sheet. When

*Fasciculus interauricularis horizontalis (Tandler, J.: Anatomie des Herzens, Jena G. Fischer, 1913).

the fibers enter the sulcus, they become surrounded by loose connective tissue in the bottom of the sulcus, continue downward the length of the groove, and extend below it, near the endocardium, toward the atrioventricular groove. In the hog, and in other animals, also, these fibers form a distinct bundle which runs to the auriculoventricular groove on the acute margin of the heart. This band is, perhaps, the bundle which French writers have described as the direct connection between

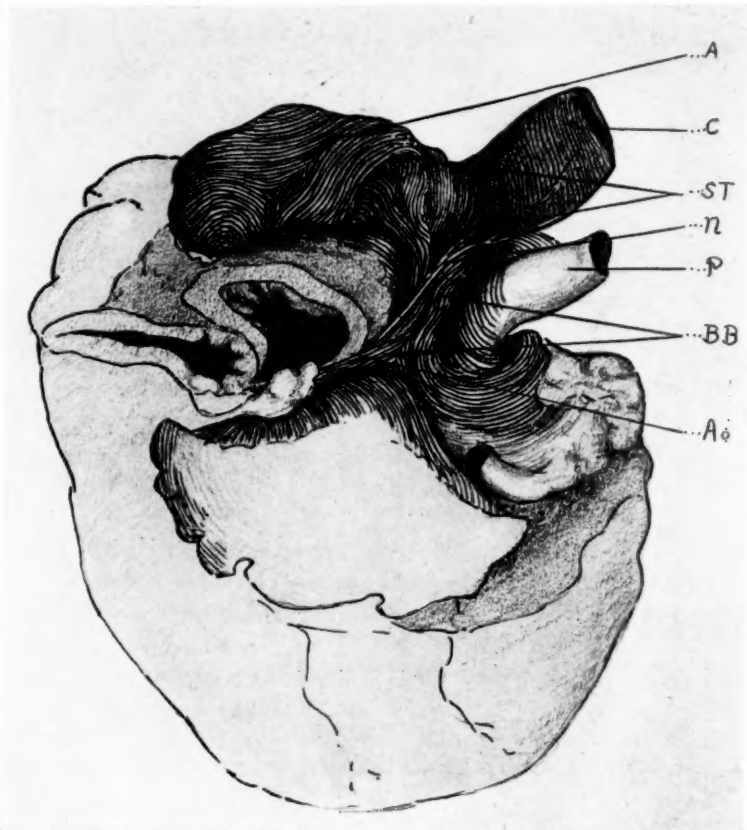

Fig. 1.—Region of the sulcus terminalis from above and behind, showing muscular arrangement of the human heart. The epicardium has been removed and the vena cava bent forward. *A*, Auricular appendage. *C*, Vena cava. *ST*, Sulcus terminalis. *N*, Nerve going up over cava. *P*, Pulmonary vein. *BB*, Bachman's bundle. *Ao*, Aorta.

the sinoauricular node and the ventricle. The fibers directly to the left and in front of those which lie in the bottom of the sulcus form the outer, left edge of the sulcus terminalis. These fibers extend downward like a sleeve, and, in the lower part of the sulcus, turn to the right. The upper fibers of the sleeve run over the cava, forming Wenckebach's bundle, and the lower ones continue backward to the left atrium. The surface of the sleeve has a mattressed appearance because of the fact that numerous connective tissue trabeculae separate the fasciculi. As the fibers of the sleeve turn to the right, over the cava, they become

the "nodal" fibers of this locality, and are separated by loose connective tissue from those, already described, which run toward the auriculoventricular groove. Thus, the nodal tissue is but a segment of the myocardium.

The arrangement of the muscle fibers in the sulcus region was practically the same in all of the species studied, although the amount of connective tissue varied. The larger the animal, the more conspicuous and widespread was the supporting tissue. It was firm and easily seen in the horse's heart, but was scarcely perceptible to the naked eye in the heart of the small dog and lamb. In the human heart it forms a tough shred which surrounds the "nodal" artery.

The architecture of the myocardium around the pulmonary veins is not essentially different from that around the superior vena cava, and, when a pulmonary vein enters the atrium obliquely, as does the cava, a sulcus is formed, and the muscle fibers therein are of the same type and are surrounded by the same kind of connective tissue as that in the sulcus terminalis.

We found that the histologic structure of the nodal region is substantially as it has been described by other investigators. The network which is so characteristic of the node of Tawara was not present in the node of Keith and Flack in the hearts that we examined. In the upper part of the sulcus the fibers run nearly parallel to the crista terminalis and are arranged in small bundles which are separated by an abundance of connective tissue (Fig. 3*B*). In cross sections through the upper part of the sulcus the fibers are cut transversely. Here the "nodal" structure occupies the entire thickness of the myocardium. It is triangular, with its base resting on the endocardium. As the amount of connective tissue lessens, toward the sides of the triangle, the peculiarities of the muscle fibers disappear. Farther down the sulcus, where the sleeve-like band of muscle turns to run across the cava, the fibers are cut obliquely or longitudinally. However, these are not the fibers which are encountered in the upper portion of the sulcus. At this level those fibers have lost the great amount of connective tissue which surrounded them, and now appear as ordinary muscle elements, next to the endocardium. The fibers that are cut longitudinally lie under the epicardium, run to the right, over the cava, and, for the most part, merge with the caval musculature (Fig. 2). A few of them, however, end in the thick walls of the vessels which lie in this region. To the left, on the other hand, the fibers continue as ordinary myocardial elements.

In the sheep and dog heart, in which the connective tissue is scant, and in the human heart, in which there is much loose connective tissue, both at the upper edge of the muscle sleeve running across the cava and in the space between it and the endocardial myocardium, many of the muscle fibers are slender and tortuous (Fig. 2). Such fine, wavy fibers also run parallel to the posterior wall of the cava in the human, canine, and ovine heart.

The number of the "peculiar" fibers in the sulcus varies with the amount of connective tissue which surrounds the caval entrance. There are very few in the dog and sheep, but many in the horse and ox. Branching of the muscle fibers of the caval region is not more frequent than in other parts of the myocardium. The striations of the fibers in this region are always indistinct, but can be seen in sections which have been properly fixed and stained (Fig. 2*B*). We have not noted any special, clear, perinuclear space, such as was described by Burian. The nuclei are round when the fibers are cut transversely, oval when they are cut obliquely, and rod-shaped when they are sectioned longitudinally, except in the case of fibers that have a diameter of four microns, or less. In such cells the nucleus is spindle-shaped. Multiple nuclei are no more frequent than in ordinary myocardial elements.

The fibers of the nodal region, therefore, differ from neighboring muscle elements in that they are slightly smaller in diameter, less distinctly striated, and more tortuous. Naturally, one raises this question: Do such differences justify calling this a region of specialized muscle? If they do, ordinary muscle elements should not possess these characteristics. In order to learn whether or not such is the case, we examined, microscopically, the heart wall at the junction of the atrium with the inferior vena cava, the coronary sinus, and the pulmonary veins, and at the junction of the pulmonary artery with the ventricle, as well as at various places in the right and left atrioventricular groove. Our observations follow:

1. Tortuous, slender muscle fibers were present in all of these places, and, indeed, in other parts of the atrial and ventricular walls. Such fibers occur frequently as bridges between the atria and the ventricles in the auriculoventricular groove of young human hearts, and also in the hearts of the other species.

2. We were, therefore, able to verify the statement, made by Kent,[20] that there are, in man and other mammals, definite muscular bridges between auricles and ventricles at various places in the auriculoventricular groove.

3. Oval and round nuclei are present in the slender muscle fibers wherever they occur.

4. The indistinct striations which are characteristic of the muscle fibers in the sulcus terminalis also occur in the muscle fibers that are surrounded by excessive amounts of connective tissue elsewhere in the heart.

The large, open vessel shown in Fig. 2, which is located either in the center or to the side of the Keith and Flack node, has usually been described as an artery. We have never found an internal elastic membrane nor the intima characteristic of an artery in this vessel. Hence, we believe that the vessel is a thick-walled vein. Many such veins were found around the cava in the hearts which we studied. Arteries were

also present, but they were much smaller, and had the structure typical of such vessels.

The most surprising feature encountered in our histologic investigation was the abundance of nerve tissue in both atria and in the auriculoventricular groove. Nerve cells and collections of nerve fibers were most numerous in bovine hearts. Ganglion cells and nerve trunks were prevalent in the epicardium of the sulcus terminalis. Collections of ganglion cells surrounded the caval ostium. Fig. 2 shows a small group of nerve cells and a large nerve trunk (human heart). Fig. 3*A*

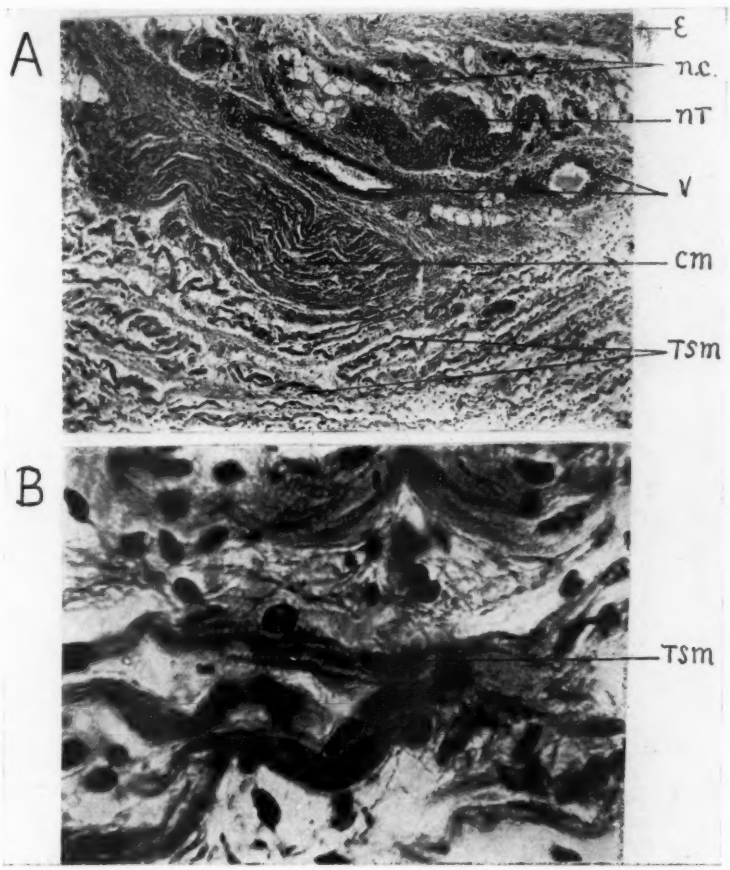

Fig. 2.—Cross section from lower half of the sulcus terminalis (human heart) (×75). In *A: E*, Epicardium. *NC*, Nerve cells. *NT*, Nerve trunk. *V*, Vein. *CM*, Caval muscle. *TSM*, Tortuous, slender, muscle fibers. In *B: TSM*, Tortuous, slender, muscle fibers, showing striations (×760).

shows a group of ganglion cells behind the cava (bovine heart). The aggregations of nerve cells consist of either small or large cells; the latter predominate. Near the entrance of the inferior cava, and to the left of it, there were huge groups of nerve cells. Scattered nerve bundles and nerve cells were found in the epicardium of the entire left atrium. Nerve fibers were also observed in the walls of all of

the pulmonary veins which were examined, and small groups of ganglion cells were found in the atrial wall near them.

In our search for muscular bridges in the auriculoventricular groove, nerve fibers and ganglion cells were found in practically all of the localities which we examined, in all of the hearts. Furthermore, as will be shown in Part II, nerve fibers and nerve cells are abundant at the top of the interventricular septum. These form a wreath of nerve tissue which surrounds the entire heart at the junction of its upper and lower chambers.

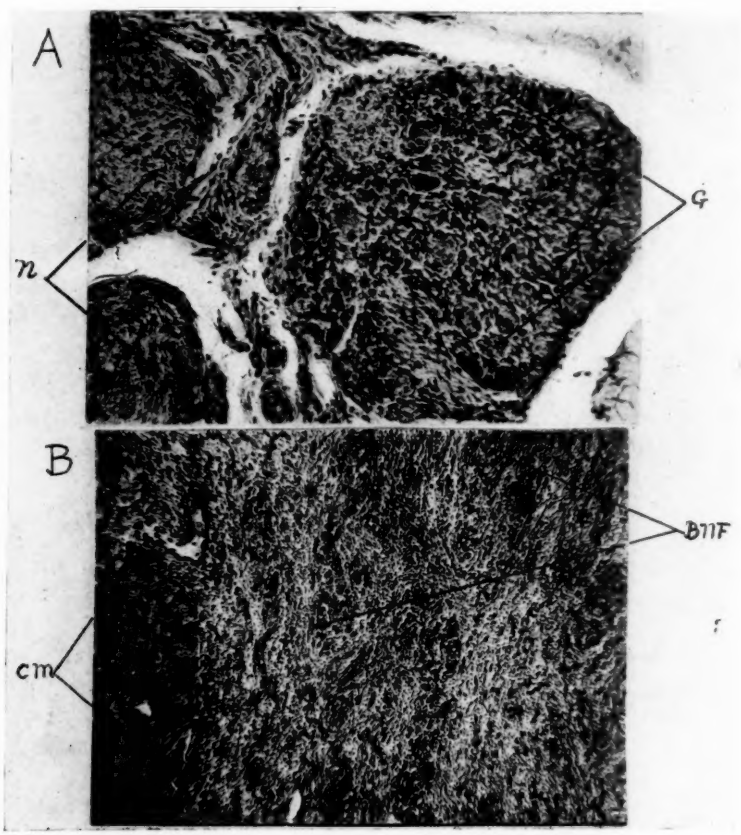

Fig. 3.—Region of the sulcus terminalis. In *A:* Bovine heart. *G*, Ganglia. *N*, Nerves. In *B:* Equine heart. Upper part of sulcus. *BNF*, Bundle of nodal fibers in dense fibrous tissue, cut transversely. *CM*, Caval muscle.

COMMENTS

It seems to us that our observations clarify many of the puzzling statements in the literature on the anatomy and physiology of the sinoatrial node. Dissection of this region discloses a stout, transverse band of muscle which runs between the bases of the right and left auricular appendages. From the right end of this band, a sheet of muscle spreads out fanlike to envelop the superior vena cava posteriorly

and anteriorly, to form the bottom and the sides of the sulcus terminalis, and to form a part of the wall of the right appendage. The part of this sheet which happens to lie in the bottom of the sulcus and its immediate neighborhood is what has been described as the node of Keith and Flack. The fact that the muscle fibers in this region become a little more slender and are less distinctly striated is to be ascribed, we think, to their environment. Hence, "nodal" muscle fibers exist on both sides of the caval entrance, as well as below and above it. This muscular arrangement accounts for the lack of agreement concerning the shape and location of the node. It also explains why those who were familiar with the histologic appearance of the fibers in this locality could always find "nodal" fibers remaining in the uninjured atrium, even after extensive destruction of the region, for the point where a given "nodal" fiber ceased to be "special" and became ordinary myocardium was purely a matter of judgment.

This study does not shed any direct light on whether the slight change which takes place in the size and structure of the fibers in the sulcus region is of such a nature as to make them the "primum movens et ultimum moriens of the heart," but it does, we believe, invalidate the general conclusions that the results of experiments on the node are exclusively myogenic. Until we exclude the possibility that the thousands of nerve fibers and ganglion cells in the walls of both auricles may affect the results, it cannot be held that the physiologic and electrical phenomena which are observed in such experiments are caused solely by muscular activity. Furthermore, these nerve elements in the atrial walls must be taken into account in any study of atrioventricular conduction, both in health and in disease.

CONCLUSIONS

1. A morphologic study of the region of the sinoatrial node in the human, equine, porcine, bovine, and ovine heart discloses the fact that the node of Keith and Flack is only a segment of a sheet of muscle which covers the first part of the vena cava superior, and spreads to the left to form the atrial myocardium.

2. The fibers of the sheet which lie in the bottom and on the sides of the sulcus terminalis become more slender and show less distinct striations when they are imbedded in connective tissue. These alterations disappear when the supporting tissue is of the same amount and type as that found in the surrounding myocardium.

3. Nerve trunks and groups of ganglion cells were found in the epicardium where the superior vena cava enters the heart, and around other veins of both atria, in all of the hearts which were studied.

4. Muscle fibers which were identical in size and structure with those in the sulcus terminalis were found in many places in both the atrial and the ventricular walls.

5. A wreath of ganglion cells and nerve fibers surrounds the heart in the atrioventricular groove.

6. Many muscular bridges between the auricle and ventricles were found in the auriculoventricular groove.

7. It is suggested that the nerve elements which are scattered profusely over the atria and in the auriculoventricular groove must be taken into account before a proper understanding of cardiac conduction, both in health and disease, can be attained.

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THE MECHANISM AND NATURE OF VENTRICULAR FIBRILLATION*

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VENTRICULAR fibrillation, first described by Ludwig and Hoffa,[1] in 1849, and called *mouvement fibrillaire* by Vulpian,[1] in 1874, is an incoordinate type of contraction which, despite a high metabolic rate of the myocardium,[2] produces no useful beats. As a result, the arterial pressure falls abruptly to very low levels, and death results within six to eight minutes from anemia of the brain and spinal cord. Abrupt apnea, followed by asphyxial gasps, pallor, cessation of all pulsations and heart sounds, and loss of all reflexes are the clinical earmarks of death from ventricular fibrillation.

Not all animals are equally susceptible, and the degree of ventricular incoordination is not equally marked. In the frog and turtle, fibrillation is induced with difficulty, and is of a coarse, undulatory type. It is generally accepted that the hearts of fowls and small mammals (mouse, rat, cat, rabbit, hedgehog, monkey) are more likely to recover spontaneously, but there are marked variations in different animals of the same species.[1] In the hearts of larger animals (dog, sheep, goat) the condition is irrevocable. We have records of over 400 cases of fibrillation in dogs, and have witnessed only a single recovery. We believe that recovery is certainly rare in man when the ventricles are entirely normal.

In mammalian hearts, it has been observed as a result of (a) experimental occlusion of a coronary vessel, (b) stimulation with prolonged, direct, alterating or faradic currents, or with brief single shocks applied late in systole, (c) the use of toxic doses of many drugs, and (d), occasionally, as a result of mechanical, chemical, or thermal irritants. So-called "spontaneous fibrillation" is probably assignable to one of these unrecognized factors.

In man, it is often a terminal event in various forms of cardiac failure; indeed, most of the published electrocardiograms were taken from moribund patients. It is apparently the cause of sudden death following the inhalation of chloroform, benzol, cyclopropane, and other vapors. It may prove to be, more often than we think, the cause of sudden death after (a) severe blows upon, or other trauma of, the chest, with or without obvious injury to the heart, and (b) in cases of stab, arrow, or bullet wounds in which death is not the result of hemorrhage and cardiac tamponade. However, *the most common causes* of human

From the Department of Physiology, Western Reserve University Medical School, Cleveland.

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ventricular fibrillation are (c) sudden occlusion of coronary vessels (usually thrombosis), and (d) electrocution, accidental or purposeful.

My own interest in ventricular fibrillation was awakened by the need of conserving laboratory animals during experimental work, for both humane and economic reasons. Although materialistic motives were an incentive to understand ventricular fibrillation and to seek means for its prevention and arrest, the hope has survived that, eventually, facts so gathered might have some practical human application.

In cardiodynamic investigations which were begun in 1912, it was necessary to stab a ventricle with the cannula of an optical manometer, or with an instrument for producing valvular lesions. In such experiments one becomes impressed with the great resistance of the heart to injury or severe manipulation. Occasionally, however—far too often, indeed—a quick stab, a slight adjustment of a trocar, or an apparently trifling insult resulted in unexpected fibrillation. It occurred in the hearts of young and old dogs alike, in hearts in good, as well as poor, dynamic and nutritive states. It gradually became evident that I was repeating experiments reported by Kronecker and Schmey,[1] in 1884, with the difference that fibrillation occurred without regard to what areas were punctured. Between 1912 and 1920, various measures were tried to avoid such disasters in experimental work, e.g., changing anesthetics or using a combination of anesthetics, cooling dogs to 30° to 32° C. before experiments were started, stimulating cardiac nerves, and employing drugs such as digitalis, quinidine, adenylic acid, etc., as prophylactics, but all were without obvious benefit.

A clue to the cause of fibrillation produced in this way began to appear in 1925,[3] during an investigation of the reactions of the ventricles to surface stimuli. May I point out that it was then demonstrated that the mammalian ventricle is not refractory to stimuli throughout systole, as is generally believed, but that it reacts during the last 0.06 second of systole by a contraction in early diastole. It is interesting to note, parenthetically, that not until 1940 were the ventricles of the frog and turtle shown to be similarly nonrefractory (Shannon and Wiggers[4]).

In our zeal to ascertain the earliest moments of responsiveness of the dog's ventricle, very strong induction shocks were sometimes used. It was found, to my disappointment—as far as studies then in progress were concerned—that fibrillation was often induced by such a single induction shock. Taken in conjunction with similar experiments of Mines[5] and de Boer[6] on the frog's heart, they seemed to indicate that late systole constitutes a period during which the ventricle is especially vulnerable to stimuli, and that the incidence of fibrillation from punctures is not a topographic, but a temporal, matter. However, the clue did not then reach a "publication threshold." Subsequently, Andrus, Carter, and Wheeler[7] induced atrial fibrillation by a single induction

shock; and Ferris, King, Spence, and Williams[8] produced ventricular fibrillation in rams by applying direct current shocks, 0.03 sec. in duration, to the chest wall during the inscription of the T wave of the electrocardiogram. This they interpreted as the partially refractory period. More recently, Wegria and I[9] demonstrated unequivocally that the application of very short condenser shocks locally to a spot on the ventricle induces fibrillation when the shocks fall during late systole, but never at any other phase of the heart cycle. We therefore designated this the *vulnerable phase* of systole. The results have now been confirmed, under various nonvolatile anesthetics, on cats and dogs, as well as on decerebrated cats. Ventricular fibrillation occurs under a wide range of dynamic conditions, including hypertension, shock, and myocardial failure, as well as during anoxia, asphyxia, and hypercapnia. How these many influences modify the threshold remains to be determined. It is induced by stimulating any spot on the ventricular surface; specific fibrillation areas do not exist. A brief rectilinear shock (ca. 0.01 to 0.03 sec.) and a single or partial sine wave are similarly effective, but only when they fall during the vulnerable period.[10, 11] More prolonged direct current or alternate current shocks induce fibrillation only when an effective moment of the stimulus falls during the vulnerable period of a normal or a premature systole.[10, 11] Spread of current is not a factor in the induction of fibrillation.[12]

Certain fundamental facts emerge from studies so far completed: (1) Fibrillation is started by a highly localized stimulus which must, however, reach a certain strength; otherwise, only a premature beat results. (2) It is not necessary to pass a current through the rest of the myocardium in order to induce fibrillation. (3) The capacity to fibrillate is inherent in heart muscle; it does not require the sensitizing action of nerves or the presence of epinephrine or related substances, although admittedly these may be found to affect the fibrillation threshold. Miss Maltby and I found, in 1929 (unpublished work), that fibrillation is easily induced in the cat's ventricle after perfusion for many hours with Locke's solution, which certainly must have washed away all traces of body hormones.

THE EVOLUTION OF VENTRICULAR FIBRILLATION

Cinematographic studies[13] strongly suggest that ventricular fibrillation cannot be adequately described as an asynchronous contraction of ultimate myocardial fractions (fibers?). The incoordination and asynchronism first involve comparatively large sections of the myocardium, which progressively multiply and decrease in size as fibrillation continues; but, even in the stage of fine fibrillation, asynchronism in the contraction of adjacent fibers does not seem to occur. The contractions are initially vigorous, but fail to elevate ventricular pressure because conduction is slow, summation of fractionate contractions is thereby

delayed, and different blocks do not contract synchronously. As myocardial anoxia develops (because of interruption of coronary flow), the vigor of contractions decreases until, within thirty to forty-five minutes, all visible signs of movement cease.

That there are four general stages, as previously described,[13] has been amply confirmed by our recent studies; but greater thought and experience suggest certain reinterpretations and amendments.

The first, or undulatory, stage, previously called the tachysystolic stage, is very short; it lasts for only a second or two. However, its analysis is highly important for the light it sheds on the mechanism which starts the fibrillation. Careful, direct observation or slow-motion pictures show that the ventricle undergoes three to six undulatory contractions which have many of the earmarks of premature systoles. The contraction wave spreads more slowly than normal, and in several directions from the area stimulated. This is represented schematically in Fig. 2*A*, in which the two dots indicate the stimulated points. A fair degree of coordination exists, in the sense that fairly large areas are excited in sequence. These contractions are slightly preceded by aberrant ventricular complexes in electrocardiograms recorded by standard leads. Consequently, I previously concluded, with other observers, that fibrillation is initiated by a short run of premature contractions, and called this the tachysystolic stage. More careful study of a large number of instances of fibrillation, particularly those induced by single shocks, favors the interpretation that only the first of these beats represents a true premature contraction, elicited by the focal stimulation. The remainder are apparently caused by re-entrant waves. In the first place, a careful re-examination of the motion pictures indicates that the surface waves of contraction do not follow quite the same path or areas. The evidence for this cannot be presented in print. Secondly, the periods of the sequential electrical deflections in the standard leads become progressively shorter, and the configuration of successive deflections changes progressively. This is illustrated by Fig. 1. In curve *A* the introduction of one sine wave (*St*) during the vulnerable period caused a single premature contraction; the complete course of the aberrant deflection is indicated by *QRT*, with a superimposed *P*. This resulted in a barely recognizable rise of intraventricular pressure (wave *E*.) When a different phase of the same shock (*St*) strikes the vulnerable period, as in curve *B*, it produces an almost identical premature electrographic deflection (QRT) and a slight rise of pressure (*E*), but this is followed by four electrical deflections of diminishing periods and different configurations. These deflections, which represent the introductory undulatory phase, change abruptly at *X*, where the convulsive stage develops. Occasionally, this undulatory stage is more prolonged, as shown in Fig. 1, Curve *C*, in which case the undulatory and convulsive stages are not so clearly demarcated. The effect of these aberrant

excitations on ventricular pressures is very variable. Sometimes only the first premature beat causes a small pressure elevation, but it may be much more definite than any shown in records illustrating this article. Occasionally, there are no changes except those which result from atrial contractions, as shown in Fig. 1*C*. Again, the second, third, or fourth beat may cause a larger rise of pressure than the first, as illustrated in Fig. 1*B*. Such effects are never observed as a result of repeated electrical stimulations during diastole, which evoke true premature beats.

The second stage, that of *convulsive incoordination*, lasts from fifteen to forty seconds. It is characterized by more frequent waves of contraction, which sweep over smaller sections of the ventricles. Each area still executes fairly powerful contractions; but, inasmuch as not all masses contract in phase, the ventricle is pulled about in a convulsive manner. The term "flutter" does not describe the appearance of these movements very well, and hence is avoided.

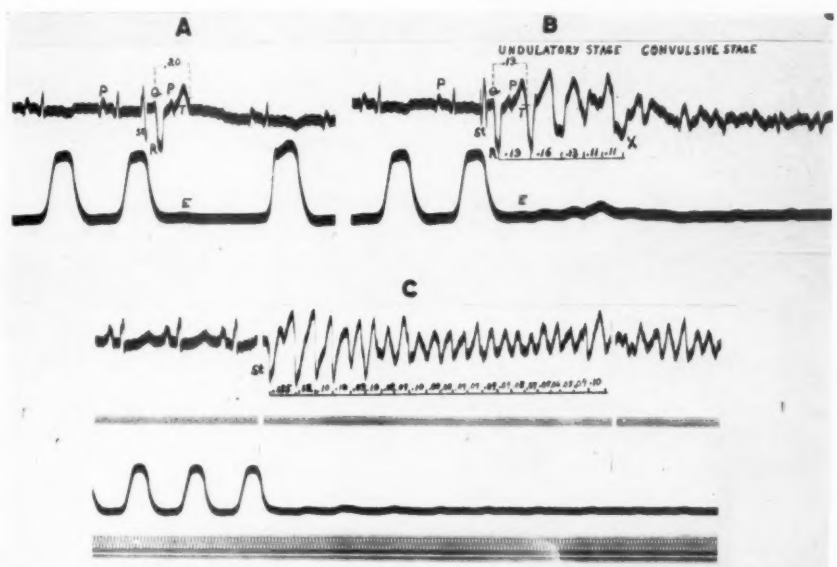

Fig. 1.—Curve *A*, Electrocardiogram (Lead II) and left ventricular pressure curves, illustrating the production of a premature beat QRT by a single sine wave (*St*), and the delayed effect on left ventricular pressure, *E*. Curve *B*, Similar records from the same experiment, showing effect of a single sine wave (*St*) during the vulnerable period of systole. Note the same initial QRT, followed by deflections of changing configuration and reduced periods. Curve *C*, Similar records from another animal showing same features except a prolongation of the undulatory stage.

The third stage, that of *tremulous incoordination (Herzzittern)*, lasts two to three minutes. The surface of the ventricles appears to be broken up progressively into smaller and smaller independently contracting areas. These multitudinous contractions of fiber groups, all out of phase, give the heart its tremulous appearance, and generally cause an increase in the frequency of electrocardiographic waves.

In summarizing these stages, one may say that ventricular fibrillation is never an asynchronous, incoordinate contraction of individual fibers, as the name implies. Rather, the incoordination and asynchronism involve smaller and smaller areas or masses of myocardium, until, in the tremulous stage, there are innumerable groups of contracting fibers.

The fourth stage, that of *atonic fibrillation,* develops when the increasing anoxia causes depression of contractile force, slows conduction, and, eventually, leads to regional blocks and complete failure of contractility. It usually develops within two to five minutes after the onset of fibrillation, and is characterized by the slow passage of feeble contraction wavelets a short distance over the ventricular surface. Progressively, more and more areas become quiescent, and, in the end, the region overlying the interventricular septum alone shows a lazy passage of waves.

THEORIES AS TO THE NATURE AND MECHANISM OF VENTRICULAR FIBRILLATION

As to the fundamental mechanism of fibrillation we have plenty of theories, but none is universally accepted. Space is lacking to review the different hypotheses, but we may note in passing that they all center around two ideas, viz., (a) that the impulses arise from centers, or pacemakers, or (b) that the condition is caused by the re-entry of impulses and the formation of circles of excitation. Each of these views, again, has two groups of exponents, viz., (a) those who believe that a single focus, or excitation ring, occurs, and (b) those who favor the idea that multiple foci, or numerous circus rings, are developed. Obviously, all of these conceptions revolve about the mechanisms which are in operation when fibrillation has been fully established; they do not deal with the processes which initiate fibrillation, or with those which explain its evolution. Although we are not yet in a position to suggest any hypotheses which satisfactorily explain either the inception or the evolution of the fibrillation process, we may profitably examine the clues which recent experimental work offers.

THE INITIATION OF FIBRILLATION

A satisfactory theory as to the onset of ventricular fibrillation must explain (a) the re-entry of impulses which causes the primary undulatory beats, and (b) the generalized disorganization of ventricular conduction by a strong, momentary stimulus which is essentially limited to one locality on the ventricular surface. It must further account for the facts (c) that a brief stimulus, or the effective portion of a prolonged one, must fall exactly in the vulnerable phase of late systole, and (d) that, if the strength of such a stimulus is inadequate, only a premature contraction results, i.e., that the conditions for re-entry and induction of undulatory beats are not created. We may profitably examine to what extent these coefficients can be explained by recent

experimental work, and state with greater exactness the problems that remained unsolved.

The demonstration that brief shocks, when applied locally to the ventricle, can cause a response, i.e., either a premature contraction alone, or such a contraction followed by undulatory beats and true fibrillation, indicates clearly that some fractions of the myocardium have passed out of their refractory state before the end of systole, which is demarcated by the incisura of ventricular or aortic pressure curves, or by the end of the T wave in the electrocardiogram. Such a probability has been previously analyzed by the author in a theory of the summation of fractionate contractions.[14] Such an asynchronous offset of fractionate contractions, caused either by the slight delay in their onset or by variations in their durations, is, as King[15] has properly emphasized, essential to any concept of the initiation of fibrillation. Unfortunately, such an analysis does not go far enough; it fails to explain why a strong, brief stimulus, when applied during the vulnerable period, induces fibrillation, whereas a similar, but weaker, shock is followed only by a single premature beat. Frankly, this question cannot now be answered, but certain facts allow us to extend the analysis into channels that may lead to new experimental ideas.

It is possible that the premature beats which are elicited by diastolic stimuli and by those applied during the vulnerable period are not initiated in exactly the same way. It is conceivable, for example, that the impulse which is initiated by diastolic stimuli at once spreads radially from a discrete focus; whereas an impulse which is started during the vulnerable period may find many adjacent fractions still refractory, and therefore weave its way to form a broader wave front during the first 0.02 to 0.03 second, i.e., until all muscle fractions have become nonrefractory. Thus, as is illustrated crudely in Fig. 2*B*, the sinuous passage of impulses from x to y may cause the formation of a wave front at y, from which the sweep of excitation responsible for the premature beat proceeds. In any event, the longer intervals between stimuli and mechanical responses and between the onset of electrical and pressure deflections in the case of premature systoles which are elicited during the vulnerable period (cf. Fig. 1*B* and *C*) suggest that there is some sort of delay in their initial spread.

The fact that only strong stimuli, applied during the vulnerable phase, are followed by undulatory waves and fibrillation can be interpreted to signify that they exert some influence at a distance, which modifies conduction and permits re-entry, or that more muscle fractions are excited under the active electrode, thereby forming a different type of wave front, from which conduction proceeds over the myocardium. Inasmuch as we are limited to analyzing only contraction and electrical phenomena on the surface of the ventricles, it is extremely difficult to obtain evidence in favor of either hypothesis. However, a priori, the

idea that a strong, brief stimulus creates a local condition responsible for re-entry of waves seems the more plausible. Even speculations as to *how* the local action of stronger currents can produce the conditions necessary for re-entry of impulses, e.g., longer pathways, slower conduction, or shorter refractory states in muscle fractions, are still difficult to formulate. We have suspected that, by stimulation of more reactive fractions, a broader wave front may be formed at *y* after stronger stimuli, and that, in this way, the wave of excitation spreads slowly over aberrant channels, perhaps muscle bundles, to the opposite ventricle, whereas with weaker stimuli the opposite ventricle is apparently excited *via* its bundle branch.[3] A forward step would be taken if it could be demonstrated that fibrillation occurs only when the impulse which is released also causes a premature summation beat of the opposite ventricle, instead of a delayed, but normal, type of contraction, such as occurs after diastolic stimuli.[3] The existence of slowed conduction and longer pathways, the two prime factors in re-entry, would thus be established.

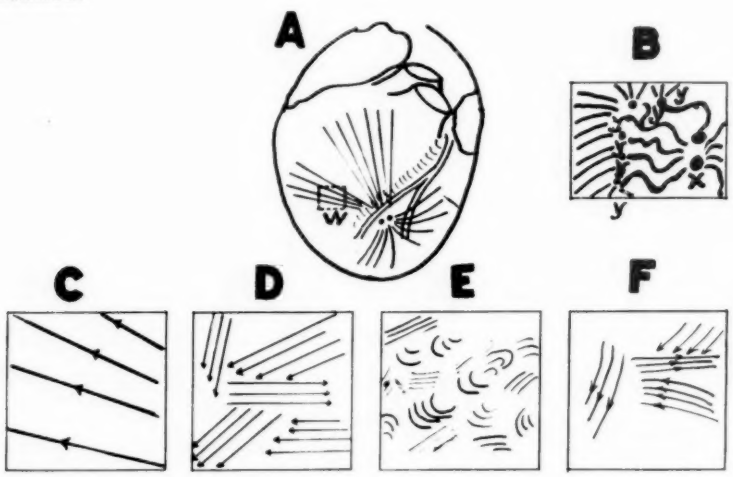

Fig. 2.—Diagrams indicating the spread of waves, observed in analysis of moving pictures, during stages of fibrillation. *A*, spread of wave front during initial, undulatory stage. *B*, Theoretical passage of impulses from point *x* to form a wave front at *y*. *C-F*, Appearance of contraction waves in small rectangular area *W*, magnified: *C*, undulatory stage; *D*, convulsive stage; *E*, tremulous stage; *F*, atonic stage.

MECHANISMS OF EVOLUTION

It may be stated at once that, in my opinion, the known experimental facts are best explained by the theory that a re-entry of impulses and formation of limited circuits occur throughout the evolution of fibrillation. However, it is necessary to amend this general statement in two respects: 1. As the fibrillation advances, the distances traveled decrease, and the number of muscle masses which are excited independently increases and becomes smaller. 2. Inasmuch as sequential excitations travel over a bulky mass of ventricular muscle, we must not

think in terms of two-dimensional rings or circuits, but rather of massive *impulse fronts* spreading in three dimensions.

During the undulatory stage we can conceive of several (probably never one) long circuits of impulse fronts which excite muscle fractions in an orderly manner, but in slow sequence. In this way, a slow recruitment of fractionate contractions occurs in several sections of the myocardium; indeed, it is not impossible that they follow muscle bundles. However, inasmuch as the summations of recruited fractionate contractions are not synchronous in different sections, the beats of the ventricles as a whole at once become ineffective, elevating intraventricular pressure only a trifle, if at all.

With the onset of the *convulsive stage* the circuits of impulse fronts abruptly become smaller, perhaps because they interfere with each other and are annihilated as wave fronts collide, and because there is some decrease in rate of conduction as a result of progressive increase in anoxia.

If, during the progressive development of fibrillation, as described above, the behavior of any definite surface region—say 2 to 4 cm. in diameter—is analyzed in the motion pictures, this area appears to be broken up progressively into smaller and smaller areas, each developing different contraction rates despite continued slowing of conduction. An attempt at static pictorial representation of what moving pictures show clearly is made in Fig. 2.

The fan-shaped lines of Fig. 2*A* serve to denote roughly the slow sweep of contractions from the point of stimulation. If a small rectilinear area such as is drawn in this figure is enlarged, we note a portion of the unidirectional sweep of the wave, as indicated in Fig. 2*C*. If such a small area is studied frame by frame, in moving pictures, we note that, as fibrillation progresses to the convulsive stage, waves begin to travel in different directions at different times, as illustrated in Fig. 1*D*. During the tremulous stage, myriads of minute wavelets seem to spread over this small area, as shown very imperfectly in Fig. 1*E*. Finally, in the atonic stage, waves of contraction spread occasionally and lazily over portions of this area, as indicated in Fig. 1*F*. If several such areas are compared, the tempos of dominant contractions are rarely related; in fact, considerable differences are usually found. Such an analysis of surface contractions by cinematographic methods is probably more precise than a study of contractions recorded by simple mechanical devices, for records so obtained are decidedly affected by shortening and lengthening in adjacent and underlying muscle. Consequently, the evidence presented by Rothberger and Winterberg[16] that the contractions in different regions are synchronous cannot be regarded as convincing. Indeed, Rothberger,[17] in reviewing this work, admits that synchronism of regional contractions is found only occasionally and, we may add, it then probably occurs fortuitously. Evidence of asynchronism

in different regions was also found by B. Kisch,[18] who registered electrical variations by two punctate leads from the ventricular surface. He found that the deflections from such areas differ as to amplitude, form, direction, and number. I have recorded similar, punctate unipolar leads simultaneously from three or four regions of the ventricles, together with a standard electrocardiogram, in fourteen dogs. Analysis of many records has shown that only exceptionally, and for brief periods, is there any synchronism of deflections. Examples are shown in Figs. 3, 4, and 5. Fig. 3 illustrates four such leads from areas indicated on the adjacent photograph of the ventricles, while the ventricle was beating normally, just before fibrillation.

Fig. 4 shows the records from the same points during the convulsive stage of fibrillation, i.e., about one minute after the induction of fibrillation. White lines, corresponding to the troughs of the standard electrocardiographic deflections, are drawn to cut the respective curves. A glance shows the lack of incidence, as well as the differences in direction, form, and amplitude, of the most nearly corresponding waves. The tempo and regularity of the major deflections are also variable. Thus, in the segment reproduced as Fig. 4, we can count nineteen to twenty-one waves in the lead from point *1*, twenty-one irregular waves in that from point *2*, thirteen rather regular deflections in the lead from point *3*, eleven variable waves in that from point *4*, and nineteen periodically variable deflections in the standard electrocardiogram (Lead II).

It is difficult to understand how such asynchronism of visible and electrical waves could occur as a result of the release of stimuli from a unitary center or a single excitation ring. This also accords with the evidence on ventricular fibrillation presented by Brams and Katz.[19] On the other hand, it is easy to explain by assuming that a wholly unorganized spread of impulses occurs, and that fields of re-entry are progressively reduced as a result of the interference of more and more impulses.

As the areas diminish in size the convulsive movements are transformed into tremulous vibrations, because the waves re-enter more frequently. The tempo of fibrillation in small areas, and therefore of the whole heart, becomes very rapid. Coincident with this breakdown into smaller areas, the frequency of fibrillating waves in standard leads increases progressively from 500 or 600 to 1,000 per minute, or more. However, variations in the tempo of local, standard, electrocardiographic deflections must be expected because of the frequent summation of the ultimate potential differences which are created by spatially separated fiber groups. Fig. 5 shows 3 punctate leads, together with a standard Lead II, during the early tremulous stage. The calculated frequency of deflection in the upper record is 840/min., in the

second, 675/min., in the third, 600/min., and, in the retouched lower curve, about 480/min.

Another factor enters, however, to explain the progressive changes of fibrillation. During the first three stages, the vigor of contraction is fairly well maintained in individual fractions. This and the frequent excitations probably account for the higher metabolic rate observed

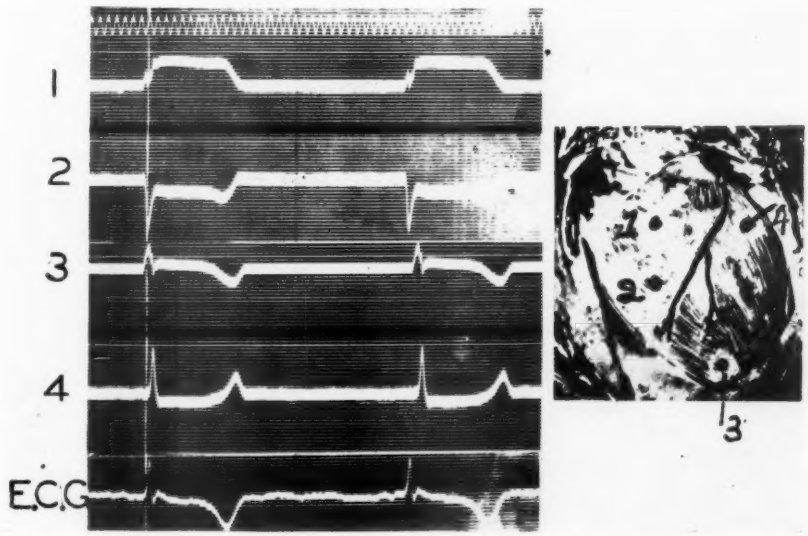

Fig. 3.—Four, punctate, unipolar leads from points on the ventricular surface, indicated by picture of heart, to right, and an electrocardiogram (Lead II) from normally beating heart.

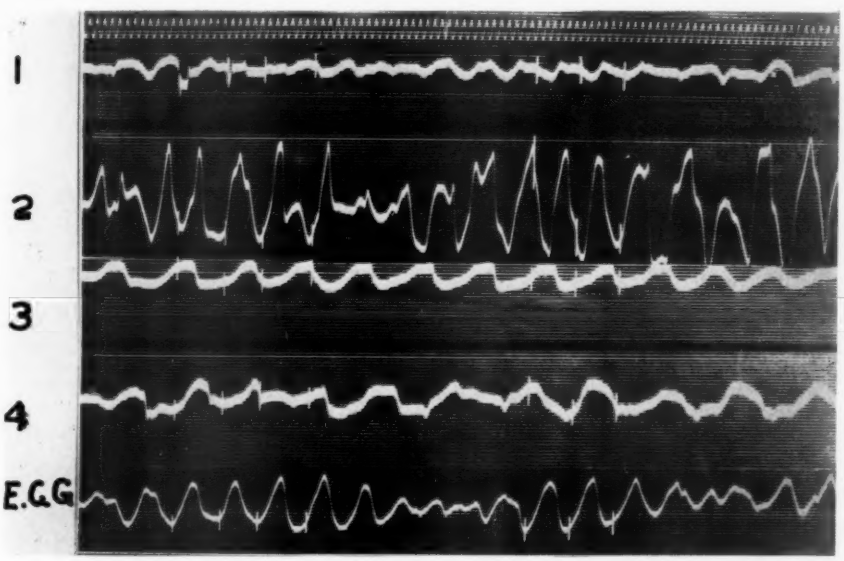

Fig. 4.—Same leads as in Fig. 3, from same heart during convulsive stage of fibrillation, i.e., thirty-nine seconds after its induction.

by Hooker and his associates.[2] However, the only readily available supply of the oxygen which is necessary for contraction is bound to myohemoglobin. The oxygen bound to the blood in the ventricles is probably of little use. As the oxygen is gradually depleted and waste products continue to accumulate because of the absence of circulation, the fractionate contractions become progressively weaker, and finally cease entirely. This explains the ultimate weakening of contractions during the atonic phase of fibrillation, which may last thirty minutes or more.

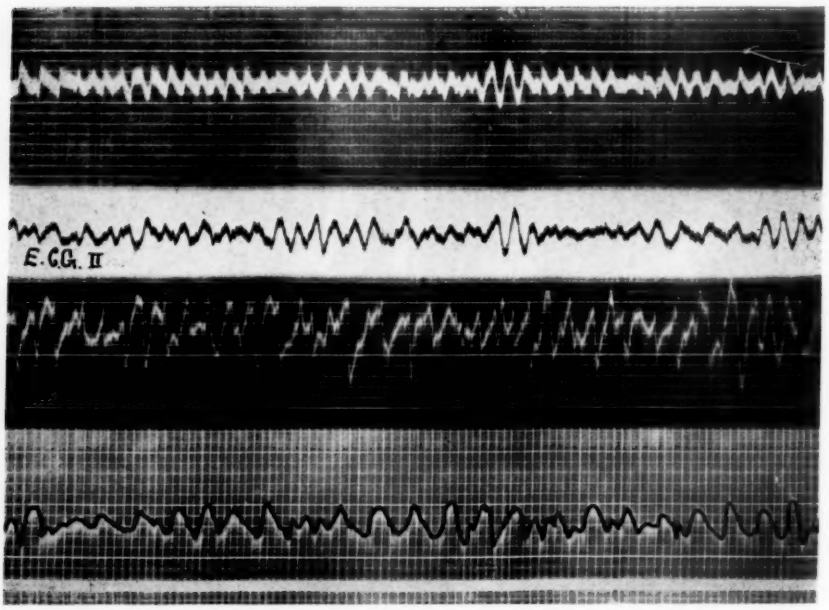

Fig. 5.—Similar leads from another heart during beginning of tremulous stage.

SUMMARY

Ventricular fibrillation, which is a common cause of sudden death following anesthesia, coronary occlusion, electric shock, etc., cannot be adequately described as an asynchronous, incoordinate contraction of ultimate cardiac fractions. The process is an evolution of changes from the moment of its inception until it ceases completely, which is within thirty to forty-five minutes.

The visible spread of waves and punctate unipolar electrocardiograms are reviewed. The available evidence favors the conclusion that, after a single premature systole, the phenomenon is caused by re-entry of circulating wave fronts which involve smaller and smaller blocks of myocardium, each of which develops an independent excitation. As a result of the anoxia which develops progressively after the cessation of coronary flow, conduction is slowed and the vigor of fractionate con-

tractions decreased. The resultant of these changes causes, in succession, the undulatory, convulsive, tremulous, and atonic stages of its evolution.

The theory which best explains these sequential changes and the initiation of fibrillation by the application of a brief, strong, localized shock during the vulnerable period of late systole may be stated briefly as follows:

In order to initiate fibrillation, an electrical stimulus or noxious influences with a "fibrillation threshold" must be applied during the vulnerable period of late systole, at which time certain elements have passed out of the refractory phase. Such a stimulus excites impulses in a number of nonrefractory fractions. These weave their way slowly through local, nonrefractory tissue to form a small wave front, from which a massive excitation wave sweeps over comparatively large portions of the myocardium in sequential order. This constitutes the first premature systole. If the wave front is large enough, and the mode of spread favorable for re-entry at, or near, the point of excitation, several circuits are formed through the ventricles; this is the undulatory stage.

In some way—possibly by collision of different excitation fronts, combined with slow conduction—these masses of myocardium are broken into smaller and smaller ones, in which divided waves re-enter more frequently. Thus the process passes successively into the convulsive and tremulous stages; during the latter there are innumerable avenues of re-entry. The atonic stage is characterized by progressive enfeeblement of contraction and gradual failure of conduction, which are the result of anoxia caused by cessation of the coronary circulation.

This theory is obviously incomplete in many details and can be expanded only through the development of more perfect methods for following the spread of impulses over the cardiac surface.

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THE PHYSIOLOGIC BASIS FOR CARDIAC RESUSCITATION FROM VENTRICULAR FIBRILLATION—METHOD FOR SERIAL DEFIBRILLATION

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THE high incidence of death from ventricular fibrillation secondary to coronary occlusion and the increasing mortality from accidental electrocution resulting from the widespread use of electrical appliances in our homes, on our farms, and in our trades and professions make the subject of ventricular fibrillation of special interest in the fields of preventive and curative medicine alike. It is obviously imperative that scientists should continue experimentation for the purpose of determining the conditions under which electric currents become dangerous, of attempting to render the ventricles less susceptible to fibrillating agents, and of devising means for the resuscitation of fibrillating hearts. While the rescue of human lives has not yet been achieved, it appears to many that we may be on the threshold of success, certainly in selected cases. However, our hope of crossing that threshold does not lie in the continuance of haphazard modes of experimentation, but in a methodical approach based on an understanding of the physiologic factors which determine success or failure in any given instance.

My own experience has convinced me that the physiologic basis for resuscitation of the ventricles from fibrillation rests firmly on the conception that ventricular fibrillation is not a constant phenomenon, but an evoluting series of changes from the moment of its inception until its natural cessation, which occurs within thirty to forty-five minutes. As was shown in the preceding communication,[1] the asynchronicity and incoordination involve progressively smaller blocks of myocardium, in which the character of the contraction alters as a result of progressive anoxia caused by cessation of coronary flow. Consequently, in devising procedures to defibrillate the heart and to restore normal modes of excitation and vigorous coordinated contractions, we must take cognizance of the state which exists at the time the procedures are applied.

For example, the atonic stage of fibrillation, in which a significant degree of anoxia causes depression of contractile force and slows conduction, develops two to five minutes after the onset of fibrillation, or appreciably earlier than irretrievable failure of the central nervous system. Although fibrillation can be readily stopped at this time, the coordinated beats which redevelop are exceedingly weak and, dynam-

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ically, useless. Consequently, one of the problems of revival consists either in finding means which can be employed within the first three minutes or in devising expedients by which more forceful beats can be restored. Naturally, the use of powerful stimulants, such as epinephrine and related substances, has suggested itself; but it was only realized through considered, fundamental studies that these substances must necessarily prove valueless because they cannot substitute for the oxygen which is lacking.

METHODS OF DEFIBRILLATION AND RESUSCITATION

As Garrey[2] has properly emphasized, the idea of earlier investigators that fibrillation is a terminal process when hearts do not recover spontaneously has been amply disproved by abrogating fibrillation in excised hearts by cooling, by reducing the mass of fibrillating tissue, or by perfusing hearts with potassium chloride solution, followed by Locke's solution. It was, therefore, not entirely unexpected that the prompt use of solutions containing an excess of potassium might likewise abolish fibrillation in the intact heart. Two problems existed, however: (1) to get the potassium ions to the fibrillating ventricle when the circulation is at a standstill and (2) either to remove the excess potassium or to neutralize it with calcium. The former was achieved in 1904 by d'Halluin,[3] who injected KCl solution into a jugular vein and then massaged the heart. Hooker,[4] following an earlier procedure of Crile, introduced a weak solution of KCl into a carotid artery under pressure, while I[5] injected it directly into the ventricular cavities. These various procedures generally proved efficacious in defibrillating the ventricles, and the subsequent use of an excess of calcium sometimes caused a resumption of spontaneous, coordinated beats. Although such occasional recoveries constituted a technical achievement of which we were once justly proud, the therapeutic methods were certainly inadequate. Looking back, they served their chief and broader purpose not in their practical usefulness, but in defining more clearly some of the requirements which must be fulfilled if the attempt at revival is to succeed. These appear to be as follows: (1) Fibrillation must cease completely in every fraction of the myocardium. If even a vestige of fibrillating muscle remains, coordinate contractions never develop. (2) Adequate pacemakers must survive in order to initiate impulses with an excitatory value which is sufficient to inaugurate coordinated contraction. (3) Not too many pacemakers—preferably one—should dominate the re-excitation of the defibrillated ventricle, for if too many act, they cause reversion to fibrillation. (4) The muscle fractions which are so excited must be capable of responding with reasonably vigorous contractions; otherwise, weak, coordinated beats result, and the heart dies in a hypodynamic state or reverts to fibrillation.

As I periodically review my own experiments on the successive use of potassium and calcium, it appears obvious why failures often occurred; indeed, it is remarkable that the method succeeded as often as it did. Potassium abolishes fibrillation, it is true, probably by rapidly depressing conductivity, but it depresses contraction and rhythmicity, as well. When calcium is used subsequently, it may reawaken too many pacemakers, with the result that the ventricles revert to fibrillation. However, if repeated revivals are realized, the animal remains in a prolonged state of hypercalcemia, which serves no good purpose. Epinephrine aids by strengthening the contractions, but it tends to reawaken multiple pacemakers and hence reversion to fibrillation.

A new epoch in resuscitation was opened when Hooker, Kouwenhoven, and Langworthy[6] showed in 1933 that the dog's ventricles can be defibrillated, and natural, coordinated beats restored, by the passage of a 60-cycle alternating current of about one ampere, for 0.1 to 5 seconds, through the heart by means of padded electrodes. Admittedly, they were preceded in this discovery by others (e.g., Prevost and Battelli, 1900), but, as is often the case in the advance of science, the greater credit properly belongs to those who place a discovery on a substantial foundation and thereby give it currency in scientific thought. We at once repeated the experiments of Hooker, et al., with many favorable results, and, by lecture and demonstration, have attempted to acquaint laboratory workers and surgeons with the procedure.

Ferris, et al.,[7] made a further contribution by showing that the method is efficacious for the unexposed hearts of larger animals, provided very strong alternating currents are applied to the chest immediately and briefly, through padded electrodes. However, the method has its limitations. All agree that recovery is rare unless the countershock is applied within the first two or three minutes after electrocution. When the fibrillation is the result of coronary occlusion, countershock is not generally efficacious even within this short period of expectancy.

In our continued use of the method we gradually began to understand the causes for failure and periodically devised slight, but essential, modifications, with the result that with proper technique revival now generally occurs even following coronary occlusion and when the fibrillation has continued for five to ten minutes. In many instances the same heart was revived five to ten times, and we have a banner experiment in which forty-one recoveries occurred in the same dog. These modifications were not haphazard but were suggested by results of other experiments which I shall briefly relate.

First, we noted that when fibrillation had continued five minutes or more, failure to recover was not caused by the fact that the ventricles could not be defibrillated, but by the incapacity of the myo-

cardium to resume vigorous beating. Massage and epinephrine generally caused reversion to fibrillation. Then Tennant and I[8] made the seemingly unrelated discovery that a region of heart muscle which has been totally deprived of its blood supply by coronary occlusion loses its contracting power within about one minute. Similarly, we found that perfusion of the ramus descendens with Locke's solution does not provide a heart which is working in the body with sufficient oxygen to keep the perfused region contracting. Apparently, the fibrillating ventricle which has been deprived of its coronary blood supply similarly loses its capacity for normal contractions within a minute or two, and, when defibrillated after that time, is capable of executing only feeble, frustrated beats. The conditions are still worse when a section of the heart has been ischemic for a time previous to the onset of fibrillation; this partly explains the less favorable effects when the fibrillation is caused by coronary occlusion. Apparently, the indications are to supply the myocardium with oxygenated blood *during the period of fibrillation*, so that, the moment fibrillation is stopped, the muscle can contract vigorously. Accordingly, I[9] suggested, in 1936, that cardiac massage be started as quickly as possible after the onset of fibrillation and be continued until the electrodes are ready to be applied to the heart. By compressing the ventricles manually about forty times per minute, the arterial pressure can be raised to approximately 60 mm. Hg, thereby furnishing oxygenated blood to the heart (*via* the coronaries) and to the central nervous system.

In 1936 I[9] reported the revival of forty dogs from a group of forty-seven, and by 1938 I[10] had records of 168 revivals out of 187 attempts. The procedure has become standard in our laboratory, and its routine use by my associates has contributed significantly to the success of their complicated experiments on the coronary circulation, so that the revivals now number at least 1,000. Recently, we have adopted the procedure of partly compressing the root of the aorta between the fingers occasionally during the manual compression of the heart, in order to send most of the expelled blood through the coronary circuit.

A second cause of failure to revive the heart is the inability to defibrillate the ventricles completely by a single shock. In order to be successful, the alternating current countershock must be very brief and strong. In addition, it must be so applied that a current of effective strength traverses the whole myocardium. In large dog hearts—and this probably applies to human hearts—this is sometimes difficult to accomplish, with the result that a small area continues to fibrillate. Very commonly this is the interventricular septum. Generally, such fibrillation is mirrored by fine movements over the septal region of the anterior ventricular surface, but occasionally no surface activity is apparent, in spite of the fact that the electrocardiogram still shows

small fibrillary waves which are easily modified by changing the position of the heart.

The experiments of Beck and Mautz[12] indicated that the injection of small quantities of metacaine or procaine into the right ventricle before using the massage and countershock is helpful in abolishing such residual areas of fibrillation and hence in restoring normal beating. We do not believe that such an adjuvant action has been crucially demonstrated for these or any other drugs. The observations of Mautz[11] that procaine reduces the irritability of the heart during diastole, and our own confirmatory evidence (unpublished) that the fibrillation threshold is reduced somewhat, do not necessarily have any relation to the ease with which single electric shocks defibrillate the ventricles. When single, strong shocks are used, there is so much variability in their capacity to defibrillate the ventricles that successful defibrillation after the use of procaine does not demonstrate an adjuvant action. In our large experience with the method, it has frequently happened that repeated shocks failed to defibrillate, and, when we were nearly ready to stop our trials, a single shock, to our surprise, became effective. Procaine may have an adjuvant action, but, before this depressant agent is generally used, more substantial evidence of its effectiveness is needed than is furnished by the methods so far devised. In any event, we were not convinced that it helped to restore normal beating, because, like quinidine, it depresses the ventricular myocardium. This was also noted by Beck and Mautz,[12] who then adopted the expedient of improving contractility by additional injections of 5 c.c. of $CaCl_2$ in heparin, a procedure which I originally advocated but have now abandoned for reasons already discussed.

SERIAL DEFIBRILLATION

During the past year Wegria and I have had remarkable success with another modification of the countershock method which we shall call serial defibrillation. This modification consists in applying to the ventricles, through padded electrodes, not one, but a series, of brief and weaker alternating current shocks. Each shock lasts less than one second, and has a strength of approximately 1.0 ampere; one or two seconds elapse between the shocks. As a rule, from three to seven such shocks suffice.

The change in technique is slight, but the effects on the fibrillary process are quite different. Each successive alternating current shock tends to merge smaller fibrillating areas into larger ones, until a convulsive state, involving larger blocks of tissue, is redeveloped. A final shock then stops the fibrillation and allows coordinated beating to be initiated by natural pacemakers. It is our impression, from many observations, that the deeper myocardium and septum are thus included in fibrillating circuits and, in consequence, that these larger

circuits are interrupted without the actual passage of currents through the deeper layers and septum, as is apparently the case with single alternating current shocks which defibrillate. In addition, the likelihood of inducing auricular fibrillation is much reduced, so that another drawback which is inherent in the use of a single, strong countershock is avoided. Since September, 1939, Dr. Wegria and I have recorded 327 revivals out of 328 attempts and have succeeded forty-one times in one dog weighing 15 kilos. In fact, death from fibrillation in dogs with exposed hearts to which serial shocks can be administered within five minutes is evidence of gross negligence.

PRESENT STATUS REGARDING APPLICABILITY

The chief value of the experimental work, so far, consists in the help it gives in orienting ourselves as to the directions in which further research may profitably proceed and as to the avenues of pursuit which appear to be less promising, if not futile. Great as our progress has been during the past two decades, seemingly insurmountable obstacles still prevent an immediate application of our current knowledge to the practical problem of defibrillating the ventricles and restoring forceful coordinated beats after accidental electric shock or coronary occlusion. However, it is as important to face these difficulties as it is to herald our advances, for further approaches can be made only when the problems confronting us are clearly delineated.

In the case of an accidental electrocution in which the patient has been rendered unconscious, pulseless, and apneic, and no heart sounds are audible, the question arises whether the ventricles are fibrillating or the heart is arrested. The latter frequently happens after the passage of very strong currents. The fear has been expressed that the use of countershock in the latter instances might start a fatal fibrillation; whereas, if the patient were left untreated, spontaneous recovery might occur. The suggestion has even been made that any emergency rescue plan should provide for suitable electrocardiographic equipment by means of which the mechanism of the heartbeat might first be ascertained. Personally, I regard this as impractical, useless, and a waste of precious moments. In the first place, there is, at present, no portable electrocardiograph which has the two requisites for such "field" use, viz., battery operation and visible recording or electroscopic arrangements. Furthermore, electrocardiograms, if they could be obtained free from skeletal action potentials, might still be indecisive, e.g., in differentiating the waves of ventricular fibrillation from those of auricular fibrillation with ventricular standstill. Finally, complete arrest of the heart is rare, and, if revival has not occurred before an electrographic picture can be examined or before countershock electrodes are put in place, the pacemakers or conducting system are irretrievably damaged, and no spontaneous recovery can be expected.

An important question which arises in relation to human emergencies is, Can sufficient current to defibrillate the ventricles be sent through the human heart by means of chest electrodes? It has been emphasized repeatedly (Hooker, et al.,[6] Ferris, et al.[7]) that, although current durations of 0.1 second suffice and are, indeed, preferable, the current passing through the heart must have a minimal intensity. Thus the minimal amount of current, when applied as one shock by direct electrodes, which will arrest fibrillation in the dog's heart lies between 0.8 and 2.0 amperes. It is therefore improbable that the ordinary alternating current, 110-volt house circuits which are usually available can yield sufficient current to defibrillate human hearts, even when electrodes are applied directly. In order to defibrillate dogs' hearts through chest electrodes, at least six to seven amperes are required, and, in the case of hearts of animals which are comparable in weight to that of man, Ferris, et al.,[7] found it necessary to apply 3,000 volts, which gave currents of twenty-five to 30 amperes. The danger* —not to mention the general unavailability—of such currents for rescue work is apparent.

Our observation that defibrillation can be accomplished in the dog by the successive application of several comparatively weak shocks suggests that further studies ought to be made on larger animals in order to ascertain whether weaker currents might not suffice if the method of serial defibrillation were used.

Even if these vicissitudes were overcome, we would still be in a race with time. To be effective when the chest is unopened, such countershocking currents must be applied within two to three minutes after the onset of fibrillation. Even when all of the equipment is at hand, speed in the execution of each step is required in order to remain within the brief time limits. If apparatus needs to be rushed to the victim, or the victim to the apparatus, attempts to rescue appear to be futile. Consequently, for the present, the chance of success is much greater in the case of patients who are already on the operating table, particularly when the chest has been opened. Such instances of fibrillation should offer the most favorable opportunity for the utilization of countershock, even after the three-minute period. An artificial coronary circulation sufficient to supply the myocardium with oxygen can be created by massaging the heart under aseptic conditions, and the subsequent application of adequate, serial countershocks should cause resumption of vigorous ventricular beating. In such attempts at revival, we should cast aside fetishes of therapy which have been proved experimentally to be unsound. No cardiac stimulant can be of service, for it cannot be expected to benefit an anoxic mammalian myocardium. It can only do harm by setting up

*Burns, injuries to the spinal cord, closure of the epiglottis, and congestion of the trachea and bronchioles are some of the harmful effects which have been noted in reviving such large animals.

multiple foci which tend to cause reversion to fibrillation. Likewise, all agents which are known to modify, or are suspected of modifying, conduction, and, therefore, recovery from fibrillation, probably do more harm than good, because of the fact that they depress an anoxic myocardium still further. There is no substitute for lack of oxygen, and the only known way to deliver oxygen through the coronary channels is by cardiac massage.

But even if the heart be revived, we may still be defeated in our race with time. Experimental evidence indicates that the central nervous system can probably not endure the complete anoxia which results from ventricular fibrillation for more than fifteen minutes, and perhaps not that long. Moreover, the possibility of reviving higher centers through elevation of blood pressure by cardiac massage is not as promising as that of reviving the ventricles, and, in the event of resuscitation, the possibility must be kept in mind that, unless revival is prompt, the recovered victim may be left in a state of mental deterioration.

A word may be added as to the possibility of restoring normal beating after fibrillation secondary to coronary occlusion. The normal dog's heart can rarely be revived unless the occlusion is removed, and this is impossible in man. But even when the vessel is again rendered patent, in experimental animals, revival is difficult unless the ischemic area is first flooded with a supply of arterialized blood through cardiac massage. Unless this is done, the fibrillation may be abolished and the remainder of the heart may beat a few times, but the ventricles quickly revert to fibrillation, probably because the ischemic area, or its margins, develop too many pacemakers.

In conclusion, although the problem of reviving human fibrillating hearts must not be considered hopeless, we must not yet allow ourselves and others to expect too much in a practical way from our present methods until the next fundamental forward step is taken, viz., provision of oxygen for the fibrillating ventricle by methods other than massage. Since we lack suggestions in this direction, it would seem more profitable for the present to direct research talents toward the problem of reducing the sensitivity of the ventricle to the agents which cause fibrillation, with the hope, eventually, of making the heart completely refractory to fibrillation.

SUMMARY

A number of procedures which can be credited with a measure of success in defibrillating the ventricles of dogs and in restoring normal, vigorous beats are reviewed. The physiologic conditions which seem to determine success or failure are analyzed and, based upon this, a modification of the countershock method, called serial defibrillation, which appears to be more uniformly successful, is described.

In dogs with exposed hearts, fibrillation can be stopped and coordinated beats re-established by passing strong alternating currents for brief intervals (0.1 to 5 sec.) through the ventricles, provided such countershock is applied within approximately two minutes. It has been estimated that, in order to achieve similar results in man by applying electrodes to the chest, 2,000 to 3,000 volts yielding currents of twenty-seven to thirty amperes might be needed; so much current would be dangerous to both operator and patient.

Hearts of dogs which have fibrillated for five to fifteen minutes may likewise be revived, provided the ventricles are rhythmically compressed by hand for about one minute previous to the application of the countershock. Frequent inability to revive the ventricles by these procedures is the result of one or more factors: (1) Failure to abolish every trace of fibrillation, (2) failure of natural pacemakers, or conduction, to survive (3) depression of muscle fractions as a result of anoxia, so that they cannot respond with sufficiently vigorous contractions after defibrillation, and (4) the reawakening of too many pacemakers, which cause a reversion to fibrillation through conflicting excitations.

As regards the first difficulty, our recent experimental work indicates that fibrillation can be more certainly abolished in every portion of the ventricle, and by the use of weaker currents, if, instead of one shock, three to seven shocks are applied at intervals of about one or two seconds. Each consecutive shock causes a coarser type of fibrillation, involving larger masses of muscle, until the final shock arrests the fibrillation completely. It is apparently not necessary for such currents to traverse the entire myocardium in order to bring about complete defibrillation. We call the procedure *serial defibrillation*. It is preferable to the use of drugs, such as quinidine, procaine, etc.; the adjuvant defibrillating action of these drugs has not yet been crucially demonstrated, but the fact that they exert a depressing action on contractility is well established.

As regards the second and third difficulties, it has been shown that the viability of pacemakers and of contracting myocardium can be assured by efficient massage which raises arterial pressure, restores coronary flow, and relieves the anoxia. Incidentally, the viability of the central nervous system tends to be maintained. The use of stimulating drugs, such as epinephrine, calcium salts, etc., cannot be expected to benefit an anoxic mammalian heart, and, after reoxygenation, usually sets up multiple pacemakers which tend to cause reversion to fibrillation.

The difficulties of meeting the conditions necessary for the revival of human fibrillating hearts are analyzed. The conclusion is reached that, although such an achievement is not impossible, we cannot anticipate remarkable results in the present state of our knowledge. For the present, it seems most profitable to attempt to discover, through

methodical research, means of rendering the ventricles less sensitive to agents which cause fibrillation, or, even better, wholly refractory to them.

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ESTIMATION OF CARDIOPULMONARY FUNCTIONAL CAPACITY BY MEANS OF OXYGEN DEBT STUDIES

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A RELIABLE objective method of testing the functional capacity of the heart and lungs has been sought by many investigators. Such a test is particularly desirable when shortness of breath or other symptoms are largely, or wholly, subjective. Diagnostic problems involving cardiopulmonary function frequently arise in cases in which there is a controversy regarding an occupational health hazard, or a claim for compensation for disability allegedly caused by occupational exposure.

All investigators agree that such a test would supplement, not replace, any of the usual diagnostic procedures. An adequate history and a careful physical examination are unquestionably of the greatest importance. It is apparent, also, that no test, however valuable, would supplant the sphygmomanometer, electrocardiograph, or roentgenogram of the chest. Nevertheless, some practical clinical procedure or instrument which will measure individual tolerance to physical activity is needed. This paper is the report of our experience with a cardiopulmonary function test originated by Gustav Nylin,[1] of Professor Jacobaeus' Clinic, in Stockholm.

Many so-called "function tests" have been tried. The most common are stair climbing, various kinds of calisthenics, weight lifting, breath holding, etc. All of them utilize some form of exercise which makes demands upon the heart and respiratory system. With certain modifications of apparatus and technique, the cardiopulmonary function test of Nylin[1] has been selected as most satisfactory. This test is concerned with increased oxygen consumption during graduated work (stair climbing). Such increased oxygen utilization has been termed the "oxygen debt" by Hill, Long, and Lupton,[2] and others. In our selection of this test, attention was paid to the often neglected requirement that the work should not exceed in amount or differ in kind from what most persons are accustomed to in normal, everyday life.

APPARATUS

The apparatus (Fig. 1) includes a stairway circuit, reclining chair, Benedict-Roth metabolism apparatus, and metronome. The total height of the stairway circuit is one meter (six steps). The chair, which is arranged for a semireclining position and placed beside the stairway circuit, may be variously adjusted for individual comfort, including headrest and armrests. The metabolism machine includes attach-

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ments for vital capacity measurements and a device for leak-testing which is used routinely in individual metabolism studies. All tests were performed by a single examiner, in a closed room removed from distracting activity and noise.

CLINICAL MATERIAL

Fifty tests were performed on forty-five subjects who were selected at random from the Montgomery Ward Clinics of Northwestern University Medical School. This series comprised thirty-nine men and six women, whose ages ranged from 17 to 71 years. Subjects were classified according to the principal diagnosis, as follows: Group 1, eight cardiopulmonary subjects; Group 2, eight pulmonary subjects; Group 3, thirteen cardiac subjects (without heart failure); and Group 4, sixteen patients without significant cardiac or pulmonary disease. In each case a complete diagnosis was based upon a thorough history and physical examination, together with such laboratory procedures as were indicated. The principal individual diagnoses may later be referred to in Charts 1, 2, and 3. In addition, 2-meter roentgenograms of the chest, electrocardiograms, thorough chemical and cytologic studies of the blood, urinalyses, and blood Wassermann or Kahn tests were done on all subjects.

Fig. 1.

METHOD

In an interview preceding the test, a chronologic occupational history, including information concerning current medication and recent or present illness, and a detailed account of the subject's activities during the preceding twenty-four hours, were obtained. Those with fever were not accepted. Likewise, those who had had alcohol, coffee, tea, tobacco, or food within the preceding two hours were rejected. With the subject comfortable in the semireclining position, blood was obtained for cytologic and chemical studies, the arm-to-tongue circulation time (Decholin) was ascertained, and venous pressure measurements were made, all by one venipuncture. A simple manometer was used to measure venous pressure, and the reference point was the level of mid-thorax. The arterial blood pressure and pulse rate were recorded

at three- to five-minute intervals until a basal level was reached; this was also done with the subject standing, in a manner similar to that previously described by Crampton[3]. After the semireclining position had been reassumed, three vital capacity measurements were obtained.

After the subject had remained in the semireclining position for fifteen to thirty minutes, a "resting" metabolic rate was taken. This served as a control for comparison with subsequent metabolism studies following exercise. The subject was then instructed to climb the stairway circuit ten times, at a rate, regulated by the metronome, of 100 steps per minute. Immediately upon completion of the exercise a second measurement of the metabolic rate was made; this extended from the beginning of the second minute after cessation of exercise to the beginning of the eighth minute. During the first half-minute of the metabolism study the pulse rate and blood pressure were recorded. Approximately twelve minutes after completion of the first exercise test, the second test, requiring twenty trips over the stairway circuit at the rate of 100 steps per minute, was carried out, following which another measurement of the oxygen consumption was made, together with single observations on the pulse rate and blood pressure. These graduated exercise tests were found by trial to be most acceptable and are hereafter referred to as the 10/100 and 20/100 Exercise Tests.

RESULTS

Individual and group responses to the exercise tests are indicated in the form of charts and graphs; in the latter they are expressed as per cent increase of oxygen consumption above the "resting" metabolic level. No detailed correlation of the various conventional diagnostic aids with the cardiopulmonary function tests was attempted; for this a larger number of cases would be necessary.

With the 10/100 Exercise Test (Graph I), the greatest individual and group oxygen debt occurred in Group 1. The amount of oxygen debt decreased progressively through Groups 2 and 3, and was least in Group 4. Group averages are shown. That of Group 4 was but 46 per cent of the average of Group 1, which means that there was a greatly increased oxygen debt in the latter group. In studying the individual responses to the 20/100 Exercise Test (Graph II), it is to be noted that seven subjects were unable to tolerate this amount of exertion (because of dyspnea). Three had both cardiac and pulmonary disease, one had silicosis and pulmonary emphysema, and three had cardiac disease alone.

In this case, therefore, group averages could not be obtained, but it is apparent that the oxygen debt in Groups 1, 2, and 3 was greatly above that in Group 4. Individual and group vital capacity measurements (Graph III) confirmed the long since established observation that pulmonary and cardiac diseases are, in general, attended with reduced vital capacity. Individual exceptions may be noted. Group averages are shown (excluding six female subjects). The average of Group 4 was considerably higher than that of any of the other groups. A spirogram which is typical of individual response to exercise is shown in Fig. 2, with brief clinical notes on the subject of the study. An increase in the respiratory rate and excursion characteristically follows the 10/100 and 20/100 Exercise Tests, and is quite marked with the latter, in which the baseline of the respiratory tracing resembles a parabolic curve.

CHART

SUBJECT			DIAGNOSIS	FUNCTIONAL CLASS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
											Cardiopulmonary
S. C.	Age Sex Wt.	54 ♂ 190	Syphilitic and arteriosclerotic heart disease	2	Laborer	Neg. K. Neg. W.	Heart: 20-25% enlarged Lungs: Passive congestion Aorta: Mod. enlarged	Left axis deviation Myocardial damage	2750 c.c.	10.6 cm.	24 sec.
J. P.	Age Sex Wt.	57 ♂ 157	Rheumatic heart disease Coronary sclerosis	2 B	Laborer	Neg. W. Doubtful K.	Heart: 20-25% enlarged Lungs: Passive congestion Aorta: Dilatation of asc. and desc. aorta	Left axis deviation Moderate myocardial damage	2400 c.c.	7.8 cm.	27 sec.
M. B.	Age Sex Wt.	58 ♂ 216	Pneumoconiosis Arteriosclerotic heart disease Syphilis		Coal truck driver	Neg. W. Doubtful K.	Heart: 20% enlarged, aortic config. Lungs: Pneumoconiosis Aorta: Normal	Left axis deviation Auricular brillation	2700 c.c.	14.0 cm.	
I. V.	Age Sex Wt.	54 ♂ 180	Cardiovascular syphilis, with aortic dilatation		Laborer	Neg. K. Neg. W.	Heart: 5% enlarged, aortic config. Lungs: Old bilateral tbc. Aorta: Dilat. and sclerosis	Left axis deviation	3300 c.c.	17.6 cm.	
L. K.	Age Sex Wt.	60 ♂ 188	Rheumatic heart disease Arteriosclerosis	2 A	Factory laborer	Neg. K.	Heart: 5-10% enlarged, mitral config. Lungs: Increased density lower ⅓ left lung Aorta: Normal	Auricular fibrillation	2775 c.c.	17.6 cm.	21 sec.
W. S.	Age Sex Wt.	37 ♂ 123	Rheumatic heart disease	2	Factory laborer	Neg. K. Neg. W.	Heart: 25% enlarged Lungs: Passive congestion Aorta: Mod. enlarged	Myocardial damage	3275 c.c.	24.0 cm.	20 sec.
J. D.	Age Sex Wt.	69 ♂ 158	Pulmonary emphysema Scoliosis Mild hypertension		Coal miner Laborer	Neg. W.	Heart: Normal size Lungs: Bilateral emphysema Aorta: Normal	Normal for age	3800 c.c.	16.8 cm.	21 sec.
S. M.	Age Sex Wt.	59 ♂ 162	Pulmonary emphysema Cardiovascular degenerative disease		Molder	Neg. K.	Heart: Right side enlarged Lungs: Emphysema and passive congestion Aorta: Normal	Ectopic beats Digitalis effect Trigeminy	2450 c.c.		

I

	BASAL		ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE, PER CENT	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	REMARKS
Subjects										
Reclining	62	125/94	0	0	0	Resting state	+04.4	60	130/98	Note exercise intolerance
Standing	70	138/108				10/100 exer. test	+60.0	90	152/106	
						20/100 exer. test				
Reclining	64	126/78	Cell pack: 43%	Sugar: 67%	0	Resting state	+25.1	64	128/80	
Standing	70	144/94		CO_2: 48.3		10/100 exer. test	+43.9	74	150/74	
						20/100 exer. test	+47.8	66	145/78	
Reclining	84	140/86	Sed. rate 60 min.:	0	Alb. ++	Resting state	+22.2	80	142/90	
Standing	84	146/94	22 mm.			10/100 exer. test	+58.1	84	162/96	
						20/100 exer. test	+73.3	96	180/108	
Reclining	78	136/90	Sed. rate 60 min.:	Icterus index:	0	Resting state	+09.0	76	138/72	Note exercise intolerance
Standing	90	144/80	34 mm.	10.0		10/100 exer. test.	+50.1	100	168/78	
						20/100 exer. test				
Reclining	96	124/88	0	0	Sugar: +	Resting state	+07.4	96	126/90	Note exercise intolerance
Standing	102	136/102				10/100 exer. test	+80.2	140	186/94	
						20/100 exer. test				
Reclining	60	142/28	0	0	0	Resting state	−04.9	60	140/28	
Standing	66	146/30				10/100 exer. test	+39.4	68	154/30	
						20/100 exer. test	+58.9	78	168/32	
Reclining	86	124/78	0	0	0	Resting state	+10.3	86	128/78	
Standing	102	130/86				10/100 exer. test	+47.5	98	136/80	
						20/100 exer. test	+69.0	112	150/78	
Reclining	60	124/66	0	0	0	Resting state	+34.7	56	112/66	
Standing	66	126/66				10/100 exer. test	+68.8	60	140/72	
						20/100 exer. test	+85.1	66	148/78	

CHART 1—

SUBJECT		DIAGNOSIS	FUNCTIONAL CLASS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
										Pulmonary
I. B.	Age 31 Sex ♂ Wt. 120	Hydropneumothorax, left Psychoneurosis		Factory worker	Neg. K. Neg. W.	Heart: Normal Lungs: Left hydropneumothorax Aorta: Normal	Normal	2150 c.c.	27.0 cm.	18 sec.
A. K.	Age 56 Sex ♂ Wt. 104	Pulmonary emphysema Slight kyphoscoliosis		Laborer No dust exposure	Neg. K.	Heart: Normal Lungs: Bilateral emphysema Aorta: Normal	Essentially normal	2050 c.c.	5.8 cm.	17 sec.
J. H.	Age 54 Sex ♂ Wt. 147	Healed fibrotic pulmonary tbc. (upper right)		Car-loading foreman No dust exposure	Neg. K.	Heart: Normal Lungs: 2 cavities in right apex and fibrosis Aorta: Displaced to right	Sinus tachycardia Essentially normal	4050 c.c.	8.4 cm.	22 sec.
J. B.	Age 60 Sex ♂ Wt. 177	Pulmonary emphysema Healed disseminated pulmonary tbc.		Mechanic Soft stone exposure	Neg. K. Neg. W.	Heart: Normal Lungs: Many calcium deposits, especially upper third Aorta: Normal	Myocardial involvement	2800 c.c.	12.0 cm.	14 sec.
L. S.	Age 71 Sex ♂ Wt. 140	Pulmonary emphysema Arteriosclerosis		Carpenter	Neg. K.	Heart: Right side enlarged Lungs: Bilateral emphysema Aorta: Normal	Minor changes	3900 c.c.	7.8 cm.	22 sec.
T. W.	Age 49 Sex ♂ Wt. 128	Congenital cysts of lungs Malnutrition		Laborer	Neg. K.	Heart: Normal Lungs: Bilateral congenital cysts Aorta: Normal	Essentially normal	2400 c.c.	6.6 cm.	16 sec.
C. D.	Age 45 Sex ♂ Wt. 148	Pulmonary emphysema		Salesman No dust exposure	Neg. K. Neg. W.	Heart: Normal; right side enlarged Lungs: Emphysema Aorta: Normal	Myocardial damage	3400 c.c.		
S. G.	Age 57 Sex ♂ Wt. 192	Silicosis emphysema Chr. bronchitis Scoliosis		Coal miner Steel worker	Neg. K.	Heart: 15% enlarged Lungs: Silicosis and emphysema Aorta: Normal	Myocardial damage	1400 c.c.		

CONT'D

BASAL			ABNORMAL			METABOLISM				REMARKS
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE, PER CENT	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	
Subjects										
Reclining	78	134/76	0	0	0	Resting state	−03.6	70	138/84	Chest pain on inspiration restricted vital capacity
Standing	100	140/94				10/100 exer. test	+29.8	78	146/88	
						20/100 exer. test	+36.3	96	152/94	
Reclining	78	110/60	0	Icterus index: 10.0	Alb. +++ Hb. +++ WBC: 10-15 RBC: 35-50	Resting state	+53.2	80	108/62	
Standing	86	114/68				10/100 exer. test	+107.6	90	160/66	
						20/100 exer. test	+107.6	94	166/70	
Reclining	115	126/80	Sed. rate 60 min.: 39 mm.	0	0	Resting state	+33.7	108	158/98	
Standing	136	164/112				10/100 exer. test	+54.0	122	174/96	
						20/100 exer. test	+68.1	132	174/94	
Reclining	86	122/86	Sed. rate 60 min.: 35 mm.	0	Sugar: +	Resting state	+22.3	84	122/86	
Standing	94	122/88				10/100 exer. test	+36.2	90	136/92	
						20/100 exer. test	+46.2	106	152/98	
Reclining	62	122/74	Sed. rate 60 min.: 38 mm.	Total chol.: 306	Alb. ++ Casts: 3-4	Resting state	+08.0	64	124/78	
Standing	70	126/80				10/100 exer. test	+19.7	70	134/78	
						20/100 exer. test	+62.1	78	140/78	
Reclining	80	110/76	0	0	0	Resting state	+23.7	74	114/80	
Standing	100	112/90				10/100 exer. test	+40.2	78	120/82	
						20/100 exer. test	+45.7	84	122/80	
Reclining	76	100/58	0	0	WBC: numerous	Resting state	+10.6	76	108/62	
Standing	86	108/70				10/100 exer. test	+43.0	88	122/70	
						20/100 exer. test	+62.0	91	130/66	
Reclining	78	104/78	0	0	Alb. + Casts: 1-2	Resting state	+10.3	80	106/78	Note exercise intolerance
Standing	84	112/90				10/100 exer. test	+82.2	86	148/88	
						20/100 exer. test				

CHART 2
CARDIAC SU

SUBJECT			DIAGNOSIS	FUNCTIONAL CLASS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
P. T.	Age Sex Wt.	51 ♂ 148	Generalized arterio-sclerosis	2A	Steam fitter 2 years exposure to flour dust	Neg. W.	Heart: not enlarged. No aortic config. Lungs: normal Aorta: sclerotic. Calcium in wall of aortic arch	Myocardial involvement	2875 c.c.	28 cm.	19 sec.
G. F.	Age Sex Wt.	57 ♂ 118	Syphilitic coronary vascular disease	2A	Boat cook No dust exposure	Pos. K. Doubtful W.	Heart: subnormal size Lungs: normal Aorta: normal	Left axis deviation Minor myocardial damage	2800 c.c.	18.6 cm.	20 sec.
A. D.	Age Sex Wt.	42 ♂ 193	Essential hypertension	I	Office clerk No dust exposure	Neg. K.	Heart: 10% enlarged. Aortic config. Lungs: normal Aorta: normal	Numerous ectopic beats Moderate myocardial damage	4800 c.c.	16.6 cm.	14 sec.
T. S.	Age Sex Wt.	63 ♂ 137	Hypertensive heart disease	I	Teamster Fireman No dust exposure	Neg. W.	Heart: 5-10% enlarged. Aortic config. Lungs: normal Aorta: normal	Left axis deviation Numerous ectopic beats Minimal myocardial involvement	3200 c.c.	15.6 cm.	16 sec.
E. Sk.	Age Sex Wt.	65 ♂ 251	Syphilitic and hypertensive heart disease	2B	Molder and coal yard work	Pos. K. Neg. W.	Heart: 10% enlarged Lungs: normal Aorta: diffuse aneurysm of asc. and desc. aorta	Left axis deviation Minor changes	2750 c.c.	22.6 cm.	24 sec.
E. St	Age Sex Wt.	65 ♂ 124	Arterio-sclerotic heart disease with hypertension	2A	Foundry and coal yard work	Neg. K. Neg. W.	Heart: normal size, shape Lungs: Rt. diaph. adhes. and pleural calcification Aorta: normal	Moderate myocardial damage	2100 c.c.	21.4 cm.	18 sec.

CHART 2

CARDIAC

SUBJECTS

CIRCULATION TIME, ARM-TONGUE (DECHOLIN)	BASAL			ABNORMAL			METABOLISM		PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING 2ND MINUTE OF METABOLISM TEST	REMARKS
		PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE			
19 sec.	Reclining	72	98/70	Cell pack: 41%	0	WBC: 10-15 per h.p.f.	Resting state	+ 8.5	72	96/70	
	Standing	78	110/80				10/100 Exer. test	+50.4	72	120/70	
							20/100 Exer. test	+62.6	80	126/74	
20 sec.	Reclining	80	96/68		0	0	Resting state	+12.5	74	106/80	
	Standing	86	104/80				10/100 Exer. test	+36.0	68	110/76	
							20/100 Exer. test	+67.1	82	122/76	
14 sec.	Reclining	74	164/98	0	0	Alb. + gran. casts 2-3/ h.p.f.	Resting state	+11.3	72	160/106	
	Standing	78	166/114				10/100 Exer. test	+57.3	78	180/104	
							20/100 Exer. test	+81.7	86	184/102	
6 sec.	Reclining	68	124/70	Cell pack: 43%	0	Sugar +	Resting state	+20.7	64	154/74	
	Standing	72	150/82				10/100 Exer. test	+55.3	72	170/74	
							20/100 Exer. test	+67.9	80	190/80	
4 sec.	Reclining	84	150/70	0	0	Alb. ++	Resting state	+10.8	80	148/80	
	Standing	94	148/80				10/100 Exer. test	+34.2	86	160/82	
							20/100 Exer. test	+48.5	96	172/82	
sec.	Reclining	72	206/130	0	0	Alb. + gran. casts 6-8/ h.p.f.	Resting state	+ 8.0	66	198-186/120	Note exercise intolerance
	Standing	84	206/146				10/100 Exer. test	+33.8	64	224/120	
							12/100 Exer. test	+62.4	74	252/122	

CHART 2—

SUBJECT			DIAGNOSIS	FUNCTIONAL CLASS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
H. M.	Age Sex Wt.	67 ♂ 164¾	Syphilitic aortitis with aortic regurgitation Previous hyperthyroidism		Shipping clerk No dust exposure	Neg. W. Doubtful K.	Heart: 35% enlarged. Aortic config. Lungs: normal Aorta: aneurysm of arch, 14 cm.	Myocardial pathology and coronary disease	3000 c.c.	12.2 cm.	48 sec.
O. P.	Age Sex Wt.	68 ♂ 250	Syphilitic aortitis with aortic regurgitation Hypertension	2B	Farmer and laborer Underground mines for two years	Neg. K. Neg. W.	Heart: enlarged to rt. and l. Lungs: normal Aorta: diffuse dilatation of asc. and desc aorta	Left axis deviation Moderate myocardial damage	2300 c.c.	16.0 cm.	33 sec.
S. P.	Age Sex Wt.	50 ♂ 203	Syphilitic aortitis	2B	Farmer and laborer No dust exposure	Neg. K. Neg. W.	Heart: enlarged to rt. and l. Lungs: normal Aorta: arch diffusely dilated, 11.5 cm.	Left axis deviation Ant. coronary artery disease Myocardial damage	2700 c.c.	18.6 cm.	35 sec.
S. B.	Age Sex Wt.	17 ♂ 133	Rheumatic heart disease Mitral insufficiency	I	Delivery boy No dust exposure	Neg. K. Neg. W.	Heart: normal size and shape Lungs: normal Aorta: normal	Right axis deviation Minor changes	2500 c.c.		38 sec. (?)
R. V.	Age Sex Wt.	52 ♀ 123½	Cardiovascular syphilis, with beginning aortic insufficiency Hypertension	2A	Hotel maid Laundress No dust exposure	Pos. K. Neg. W.	Heart: not enlarged Lungs: normal Aorta: diffusely dilated	Left axis deviation Myocardial involvement with coronary disease	2100 c.c.	11.4 cm.	22 sec.
G. B.	Age Sex Wt.	50 ♀ 192	Essential hypertension	2A	Housewife No dust exposure	Doubtful K. Neg. W.	Heart: normal size and shape Lungs: normal Aorta: normal	Left axis deviation Minor changes	3150 c.c.	17.4 cm.	14 sec.
F. L.	Age Sex Wt.	49 ♂ 155	Syphilitic aortitis with aneurysm of descending aorta	2B	Farmer, brick work	Pos. K. Neg. W.	Heart: 15-20 % enlarged Lungs: mild congestion Aorta: aneurysm of descending aorta	Left axis deviation Minor changes	3100 c.c.	6.4 cm.	12 sec.

CONT'D

BASAL			ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE (%)	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING 2ND MINUTE OF METABOLISM TEST	REMARKS
Reclining	68	144/26	0	0	Alb. + +	Resting state	+29.1	72	168/26	
Standing	82	126/18			Sugar +	10/100 Exer. test	+79.8	86	198/46	
					Hb. +					
					RBC: 2-3/ h.p.f.	20/100 Exer. test	+79.8	80	202/42	
					WBC: 30-40 h.p.f.					
Reclining	52	164/104	Cell pack: 41%	Total chol.: 358	Alb. + +	Resting state	- 4.0	53	164/112	
Standing	60	180/116		Icterus index: 10.0	Gran. casts: 4-6/ h.p.f.	10/100 Exer. test	+40.3	72	180/112	
						20/100 Exer. test	+42.4	80	186/120	
Reclining	80	138/94	0	0	Alb. +	Resting state	+10.2	80	156/92	
Standing	84	160/100				10/100 Exer. test	+25.4	84	166/100	
						20/100 Exer. test	+25.4	92	172/104	
Reclining	80	112/80	0	0	0	Resting state	0	76	120/82	
Standing	100	112/90				10/100 Exer. test	+11.0	70	130/94	
						20/100 Exer. test	+17.2	74	112/84	
Reclining	60	166/100	0	0	Alb. + +	Resting state	+14.5	60	180/108	
Standing	68	182/112			WBC: 30-40 per h.p.f.	10/100 Exer. test	+40.7	58	206/108	
						20/100 Exer. test	+45.6	78	212/108	
Reclining	92	170/100	0	0	Alb. +	Resting state	+23.7	94	178/100	Note exercise intolerance
Standing	98	208/110				10/100 Exer. test	+54.7	114	216/102	
						20/100 Exer. test				
Reclining	60	112/68	0	0	0	Resting state	+ 6.8	56	112/68	Note exercise intolerance
Standing	68	124/78				10/100 Exer. test	+26.6	60	120/70	
						20/100 Exer. test				

CHART 3

PATIENTS WITHOUT SIGNIFICANT CAR

SUBJECT		DIAGNOSIS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
J. F.	Age 21 Sex ♂ Wt. 152	Detached retina	Clerk	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	5200 c.c.	8.0 cm.	12 sec.
W. F.	Age 24 Sex ♂ Wt. 172	Left indirect inguinal hernia	Clerk	Neg. K.	Heart: Upper limit of normal size Lungs: Normal Aorta: Normal	Minimal changes	5600 c.c.	20.8 cm.	24 sec.
V. C.	Age 29 Sex ♂ Wt. 130	Chronic posterior urethritis	Laborer	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	2800 c.c.	13.6 cm.	25 sec.
F. B.	Age 61 Sex ♂ Wt. 174	Scalp wen Syphilis	Teamster	Pos. K. Neg. W.	Heart: Upper limit normal size Aortic config. Lungs: Sl. fibrosis Aorta: Tortuous	Normal	3675 c.c.	14.4 cm.	14 sec.
A. L.	Age 39 Sex ♂ Wt. 137	Internal hemorrhoids	Salesman	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	3800 c.c.	12.2 cm.	18 sec.
P. B.	Age 57 Sex ♂ Wt. 130	Indirect inguinal hernia Varicose veins	Clerk	Neg. K.	Neart: Normal Lungs: Right hilar calcification Aorta: Normal	Normal	3600 c.c.	4.0 cm.	17 sec.
L. S.	Age 33 Sex ♂ Wt. 150	Left ureteral calculus Hernia	Clerk	Neg. K.	Heart: Upper limit normal size Lungs: Normal Aorta: Normal	Minimal changes	3800 c.c.	15.6 cm.	22 sec.
K. S.	Age 28 Sex ♂ Wt. 141	Chronic gonorrhea Urethral stricture Syphilis	Laborer	Pos. K. Neg. W.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	3650 c.c.	12.6 cm.	20 sec.
B. P.	Age 26 Sex ♂ Wt. 165	Neuro-dermatitis	Laborer	Neg. W.	Heart: Normal Lungs: Normal Aorta: Normal	Minimal changes	3925 c.c.	13.4 cm.	
O. K.	Age 36 Sex ♂ Wt. 155	Constipation Refractive error	Taxi driver	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	3350 c.c.		

3

CARDIAC OR PULMONARY LESIONS

BASAL			ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE (%)	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BLOOD PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	REMARKS
Reclining	84	118/76	0	CO_2:	Casts:	Resting state	+11.7	82	120/78	
Standing	104	130/96		40%	3-5	10/100 Exer. test	+14.0	90	126/80	
						20/100 Exer. test	+20.4	94	130/86	
Reclining	66	112/70	0	0	0	Resting state	+04.4	68	112/68	
Standing	86	112/80				10/100 Exer. test	+17.7	66	124/76	
						20/100 Exer. test	+33.3	70	126/70	
Reclining	62	112/80	0	0	Alb. ++	Resting state	−04.9	60	114/86	
Standing	68	124/90			RBC: many	10/100 Exer. test	+21.3	64	134/88	
					WBC: many	20/100 Exer. test	+21.3	66	134/80	
Reclining	72	76/56	0	CO_2:	Alb. +	Resting state	−11.0	68	112/70	
Standing		"Reaction" to decholin?		38.4	Sugar: +	10/100 Exer. test	+14.6	72	130/74	
					Gran. casts many	20/100 Exer. test	+23.2	78	138/78	
Reclining	82	114/80	0	0	0	Resting state	−02.7	84	118/78	
Standing	96	120/92				10/100 Exer. test	+13.8	86	126/80	
						20/100 Exer. test	+23.5	96	134/82	
Reclining	74	114/78	Sed. rate	0	0	Resting state	+10.3	72	118/78	
Standing	86	126/86	60 min.: 25 mm.			10/100 Exer. test	+42.1	76	126/84	
						20/100 Exer. test	+42.1	88	132/82	
Reclining	60	90/58	0	0	Alb. ++	Resting state	+07.5	62	108/66	
Standing	84	100/78			Hb. +	10/100 Exer. test	+11.1	74	118/78	
					RBC: 10-15	20/100 Exer. test	+31.5	88	128/76	
					WBC: 25-30					
Reclining	68	114/74	0	Sugar: 67	0	Resting state	+12.3	66	116/72	
Standing	96	122/90		CO_2: 47.4		10/100 Exer. test	+29.4	66	126/70	
						20/100 Exer. test	+33.0	72	132/76	
Reclining	54	118/70	0	CO_2:	Alb. ++	Resting state	0.0	54	118/72	
Standing	74	120/85		43.7	Casts: 15-20	10/100 Exer. test	+33.8	54	130/70	
						20/100 Exer. test	+42.6	58	140/72	
Reclining	62	106/70	0	0	0	Resting state	−09.9	64	108/72	
Standing	74	110/82				10/100 Exer. test	+10.9	58	106/68	
						20/100 Exer. test	+18.3	60	108/68	

CHART

SUBJECT			DIAGNOSIS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
J. A.	Age Sex Wt.	47 ♂ 145	Central nervous system syphilis Optic atrophy	Laborer	Pos. K. Neg. W.	Heart: Normal Lungs: Normal Aorta: Slightly widened	Normal	2800 c.c.	6.4 cm.	12 sec.
C. H.	Age Sex Wt.	50 ♂ 144	Questionable mitral regurgitation	Salesman	Neg. K.	Heart: Normal Lungs: Sl. emphysema Aorta: Prominent ascending portion	Minimal changes	3100 c.c.	12.7 cm.	23 sec.
A. S.	Age Sex Wt.	30 ♀ 98	Hay fever	Housewife	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	2450 c.c.	6.8 cm.	12 sec.
M. S.	Age Sex Wt.	45 ♀ 128	Psychoneurosis Scoliosis	Factory worker	Neg. K.	Heart: 15% enlarged, config. uncertain Lungs: Normal Aorta: Normal	Normal	3100 c.c.	6.6 cm.	14 sec.
L. H.	Age Sex Wt.	38 ♀ 155	Uterine fibroids Tertiary syphilis	Housewife	Neg. K. Neg. W.	Heart: 5-10% enlarged, aortic config. Lungs: Normal Aorta: Normal	Normal	2650 c.c.	16.0 cm.	12 sec.
M. F.	Age Sex Wt.	37 ♀ 128	Chronic cholecystitis	Factory worker	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Minimal changes	2750 c.c.	7.2 cm.	12 sec.

Detailed individual studies are presented in Charts 1, 2, and 3. The response of the pulse rate to exercise was found to be variable in all groups. According to Katz, et al.[4] "it is well known that the reaction of the cardiac rate and blood pressure to exercise may show wide variations, even in normal persons." We found that their use as a criterion of response to exercise was particularly unreliable in many of our subjects who had auricular fibrillation or premature systoles, and when there was apprehension or anxiety. In one subject (O. K., Group 4), a moderate decrease in pulse rate was accompanied by a slight fall in blood pressure. A study of basal pulse rates and blood pressures in the semireclining and standing positions revealed no marked deviation from the normal variations described by Crampton. When the vital capacity was subnormal, there was usually an increased oxygen debt, and vice versa, although several exceptions may be noted.

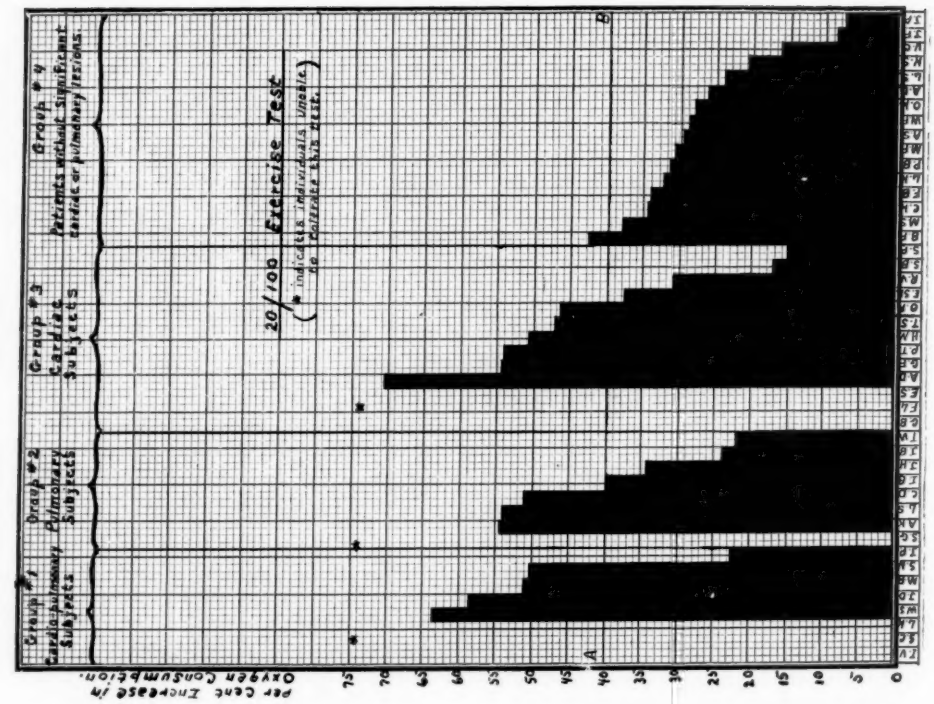
2—CONT'D

BASAL			ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE (%)	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BLOOD PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	REMARKS
Reclining	62	96/66	0	0	0	Resting state	+10.6	60	100/70	
Standing	76	110/80				10/100 Exer. test	+11.9	60	108/68	
						20/100 Exer. test	+18.3	72	112/70	
Reclining	52	90/62	0	0	Alb. +	Resting state	+08.8	50	102/70	
Standing	64	106/78				10/100 Exer. test	+18.1	52	110/70	
						20/100 Exer. test	+43.3	60	116/68	
Reclining	70	94/60	Hb: 12.6 Gm.	0	0	Resting state	+22.6	72	94/64	
Standing	80	104/70	Cell pack: 39.0%			10/100 Exer. test	+52.4	66	108/60	
			Vol. index 1.09			20/100 Exer. test	+52.4	90	110/64	
Reclining	72	126/78	Cell pack: 43.0%	CO_2: 43.6	0	Resting state	+16.6	84	126/86	
Standing	84	138/94	Col. and vol. index: 1.07			10/100 Exer. test	+51.5	66	130/78	
						20/100 Exer. test	+54.6	74	132/72	
Reclining	76	110/78	0	Icterus index: 10.0	0	Resting state	+14.2	76	114/76	
Standing	86	118/80				10/100 Exer. test	+30.0	78	124/80	
						20/100 Exer. test	+46.7	86	128/76	
Reclining	84	106/64	0	CO_2: 38.4	0	Resting state	+16.9	76	112/76	
Standing	120	96/80				10/100 Exer. test	+46.4	88	120/76	
						20/100 Exer. test	+47.9	102	126/74	

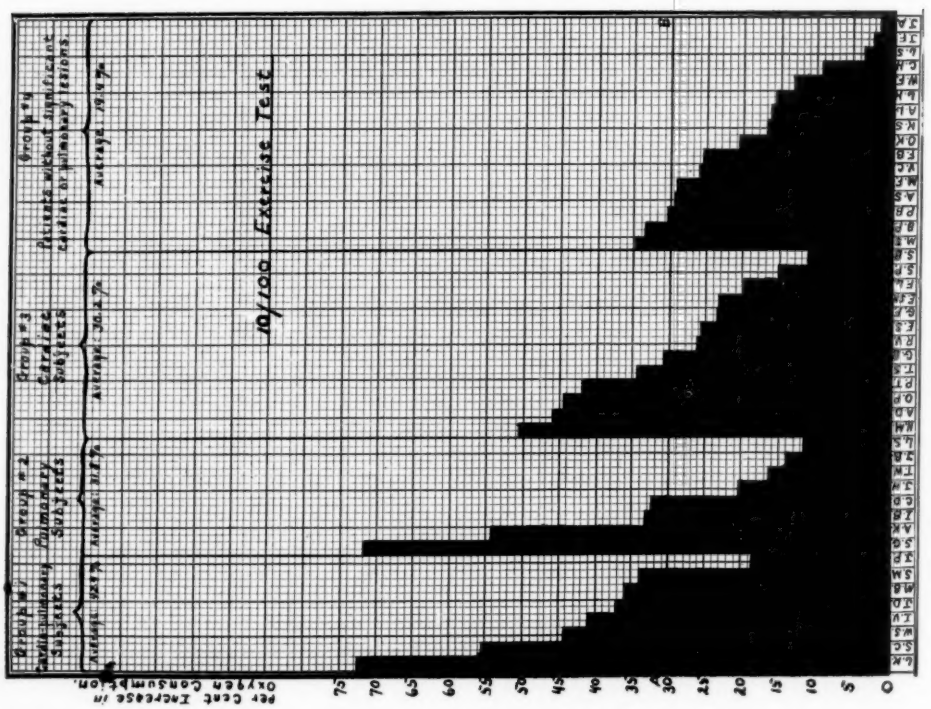
Repeat exercise tests (Chart 4) were done on five subjects representing Groups 1, 3, and 4. When the results of the repeat test are compared with those of the original test, a significant uniformity of response is apparent. Arnett and De Orsay,[5] and others, have pointed out how variable the vital capacity is, and conclude that measuring it is principally useful for making comparisons from time to time in the same patient. The results of our repeat cardiopulmonary function tests indicate, likewise, that comparison of two or more tests on one subject is of greater value than the results of any single test, for individual responses, even in a selected series of single tests, are rather widely variable.

COMMENT

The weak link in any cardiopulmonary function test is its interpretation. The best that can be hoped for in using such a test is to obtain

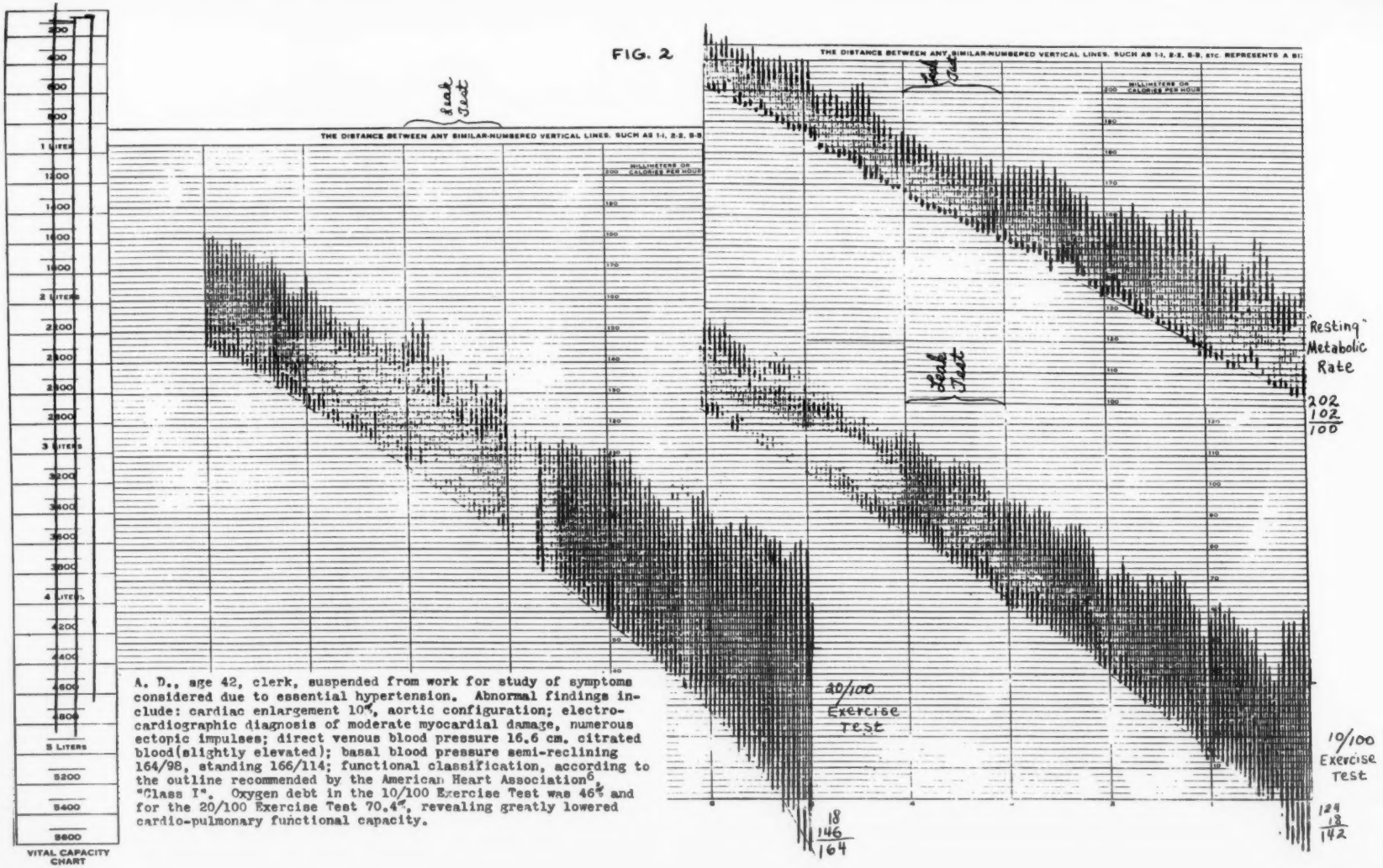

20/100 Exercise Test
(* indicates individuals unable to complete this test.
Group #1 Cardiopulmonary Subjects
Group #2 Pulmonary Subjects
Group #3 Cardiac Subjects
Group #4 Patients without significant cardiac or pulmonary lesions.
Per Cent Increase in Oxygen Consumption.
A
B

Graph II.


10/100 Exercise Test
Group #1 Cardiopulmonary Subjects
Group #2 Pulmonary Subjects
Group #3 Cardiac Subjects
Group #4 Patients without significant cardiac or pulmonary lesions.
Per Cent Increase in Oxygen Consumption.
A
B

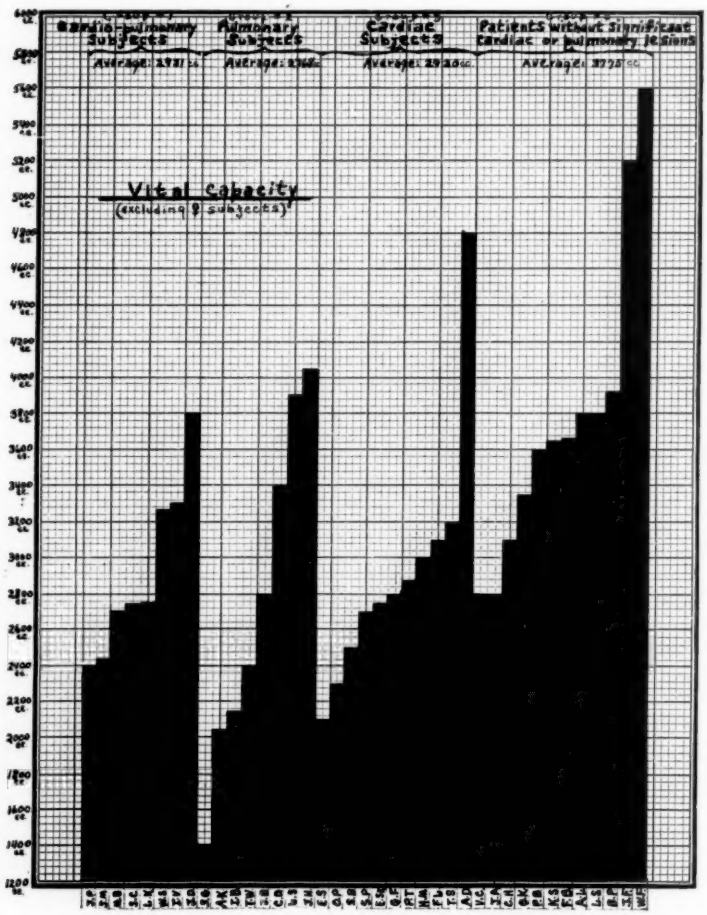
Graph I.

FIG. 2



A. D., age 42, clerk, suspended from work for study of symptoms considered due to essential hypertension. Abnormal findings include: cardiac enlargement 10%, aortic configuration; electrocardiographic diagnosis of moderate myocardial damage, numerous ectopic impulses; direct venous blood pressure 16.6 cm. citrated blood(slightly elevated); basal blood pressure semi-reclining 164/98, standing 166/114; functional classification, according to the outline recommended by the American Heart Association[6], "Class I". Oxygen debt in the 10/100 Exercise Test was 46% and for the 20/100 Exercise Test 70.4%, revealing greatly lowered cardio-pulmonary functional capacity.

a reliable indication of the subject's ability to tolerate work at the time the work is performed. In many instances, no prognosis can be made from the results obtained. In the evaluation of tests involving measurements of the metabolic rate, it is essential to control, as much as possible, factors which may give rise to misleading results. The preliminary preparation of our subjects included an intensive search for factors which might affect the metabolism studies adversely. In addition, the age, sex, state of nutrition, and occupational history were considered in each case. The type of test which we used requires a measurable



Graph III.

expenditure of energy at a definite rate. Faster rates were found to be unreliable. Many "effort" tests, such as hopping, calisthenics, and stair climbing, without accurate timing, do not stress the important factor of uniformity of response. One subject may respond with vigor, and another in a lazy manner. This raises the question of variation in the amount of energy expended. The use of the metronome assures one of

CHART 4

REPEAT EXERCISE TESTS

SUBJECT	AGE	DATE	BASAL METABOLIC RATE			VITAL CAPACITY	REMARKS
			RESTING STATE	10/100 EXERCISE TEST	20/100 EXERCISE TEST		
1. W. S.	37	8/29/39	–04.9%	+39.4%	+58.9%	3275 c.c.	Cardiopulmonary.
W. S.	37	8/31/39	–05.1%	+39.1%	+58.6%	3025 c.c.	No significant interval history.
2. M. B.	58	8/24/39	+22.2%	+58.1%	+73.3%	2700 c.c.	Cardiopulmonary.
M. B.	58	8/31/39	+29.6%	+72.2%	+90.4%	2850 c.c.	More dyspnea at rest. Longer rest necessary for basal pulse rate.
3. V. C.	29	6/22/39	–04.9%	+21.3%	+21.3%	2800 c.c.	Pt. without cardiac or pulmonary disease.
V. C.	29	9/ 5/39	–10.5%	+31.9%	+31.9%	3100 c.c.	No significant interval history.
4. K. S.	28	6/22/39	+12.3%	+29.4%	+33.0%	3650 c.c.	Pt. without cardiac or pulmonary disease.
K. S.	28	8/17/39	+05.0%	+35.2%	+38.8%	3600 c.c.	No significant interval history.
5. G. F.	57	6/ 1/39	+12.5%	+36.0%	+67.1%	2800 c.c.	Cardiac.
G. F.	57	8/31/39	+09.3%	+41.8%	+62.5%	2900 c.c.	Severe precordial pain 2 weeks earlier.

a uniform response. The variability of pulse rate and blood pressure following exercise causes one to question the results of tests which are based solely upon such observations. Any test in which the subject is required to do work is influenced not only by the functional capacity of the heart, but also by extracardiac factors, prominent among which are the respiratory functional capacity and the physical fitness of the subject. It has been our observation that in most instances it is difficult to carry out a test of cardiac function which does not, at the same time, constitute a test of pulmonary function. Hence, the term "cardiopulmonary function test" appears correct.

It is obviously difficult to define a standard of accomplishment for any particular group of subjects. A wide range of variation for normal persons must necessarily be adopted. The lines *A*—*B* in Graphs 1 and 2 represent arbitrary "upper limits of normal." Conservative opinion suggests that a given response should be considered abnormal only if the oxygen consumption increase exceeds this "limit" by 10 per cent. Attention is again drawn to the advantage of comparing tests made on the same person from time to time.

SUMMARY

The response of forty-five persons with, or without, cardiac, pulmonary and combined cardiopulmonary disease to a modified stair-

climbing exercise test has been studied, and the "oxygen debt" measured.

The results have been compared with those of other types of function tests, and the limitations of interpretation pointed out.

Although the series of cases is small, the results indicate that the test is important as an objective method of evaluating diminution in cardiopulmonary reserve.

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THE COMBINED USE OF OUABAIN AND DIGITALIS IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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A METHOD of digitalization which will rapidly produce an effective therapeutic concentration of the drug in the body, and maintain this level thereafter, is presented.

Theoretic considerations concerning the production of complete digitalization with the accepted, rapid methods are represented schematically in curves *A* and *B*, of Fig. 1. When a single dose of digitalis is given by mouth, there is a definite latent period of two to five hours before any effect is apparent,[1, 2, 3] and it takes six hours for the maximum effect to develop (see curve *A*, Fig. 1). When doses are repeated according to the method of Eggleston,[4] the full therapeutic effect is not manifest before twelve to twenty-four hours.

The disadvantages of the oral use of digitalis are: (1) the length of the latent period before any effect, or the therapeutic one, becomes apparent and (2) the necessity of repeating smaller doses under careful supervision in order to produce complete and safe digitalization. Its advantage is the slow rate of elimination from the body, which allows persistence of its action for as long a period as ten to fourteen days, and facilitates the establishment of a maintenance dose.

Ouabain (g-strophanthin), when administered intravenously, as demonstrated by Wyckoff and Goldring,[5] exerts an "initial effect in from five to twenty minutes, and a maximum effect in from fifteen to fifty minutes" (see curve *B*, Fig. 1). By giving an initial dose of 0.5 mg. of ouabain intravenously, and doses of 0.1 mg. at intervals of one-half to one hour thereafter, complete digitalization can be obtained in from one and one-half to three hours. Although the action of ouabain is rapid, it has the disadvantage of being eliminated quickly.[5, 6] Because of the fact that we do not know how much of the glucoside there is in the body twenty-four hours after its administration, the dose of digitalis which is necessary to maintain the desired effect is difficult to ascertain.

We have attempted to avoid the disadvantages of both drugs by supplementing and maintaining the early action of ouabain by the simultaneous administration of a single dose of digitalis. It was to be expected that at the time when the therapeutic effect of the ouabain passed its maximum and started to diminish, the slowly increasing

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action of the digitalis would become manifest (see curve *C*, Fig. 1), and that there would be no interval between complete digitalization and the establishment of a maintenance dosage of digitalis.

This principle, whereby a desired therapeutic effect is obtained quickly with a rapidly absorbed drug, and thereafter maintained with a drug which is more slowly absorbed and excreted, has been applied, also, in the field of anesthesia, and more recently, by Sollmann and his coworkers,[7] to antisyphilitic therapy with bismuth preparations.

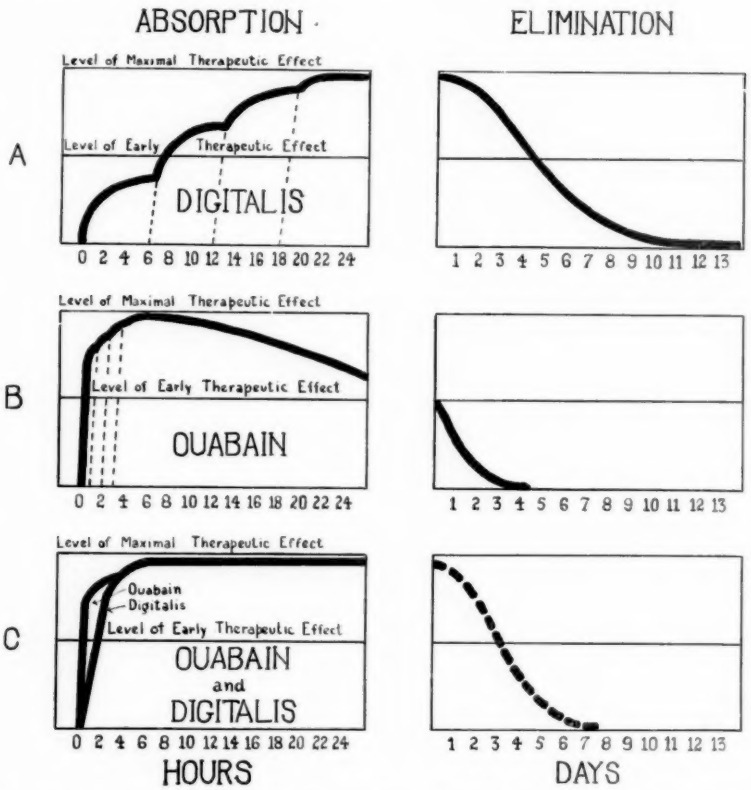
ABSORPTION
ELIMINATION
A
Level of Maximal Therapeutic Effect
Level of Early Therapeutic Effect
DIGITALIS
0 2 4 6 8 10 12 14 16 18 20 22 24
1 2 3 4 5 6 7 8 9 10 11 12 13
B
Level of Maximal Therapeutic Effect
Level of Early Therapeutic Effect
OUABAIN
0 2 4 6 8 10 12 14 16 18 20 22 24
1 2 3 4 5 6 7 8 9 10 11 12 13
C
Level of Maximal Therapeutic Effect
Ouabain
Digitalis
Level of Early Therapeutic Effect
OUABAIN
and
DIGITALIS
0 2 4 6 8 10 12 14 16 18 20 22 24
1 2 3 4 5 6 7 8 9 10 11 12 13
HOURS
DAYS

Fig. 1.—Schematic representation of absorption and elimination, *A*, of Digitalis leaf, given orally by method of Eggleston, *B*, ouabain, given intravenously by method of Wyckoff and Goldring, and *C*, digitalis and ouabain in combination. (By elimination is meant the persistence of digitalis effect upon the ventricular rate of patients with auricular fibrillation). The curve of "Elimination" in *C* (broken line) is at present under investigation.

SELECTION OF MATERIAL

Patients were selected as follows: (1) Only those patients whose heart disease could be classified etiologically in accordance with the criteria[8] established by the New York Heart Association were included. (2) During the period of hospitalization the patient must have had some or all of the following evidences of congestive heart failure: dyspnea, orthopnea, congestion of the lungs, a palpable liver, accumulation of fluid in body cavities, or peripheral edema. (3) Patients with recent myocardial infarction were excluded except in two instances. (4) Patients who had received

digitalis within the previous two weeks were excluded. (5) Patients with paroxysmal arrhythmia, but without congestive heart failure, were not included. (6) It was necessary that all patients treated be cooperative, and capable of taking medication by mouth and of giving information regarding subjective changes.

As is seen in Table I, all etiologic types of heart disease were treated, regardless of rhythm, bundle branch block, valvular deformity, or degree of congestive heart failure. The ages of the patients ranged between 28 and 79. Eight patients with myocardial infarction were studied, but, as has already been mentioned, only two had had recent infarction.

The severity of the congestive heart failure in each case, prior to digitalization, was estimated by taking into account (1) the general appearance of the patient, i.e., the degree of dyspnea, orthopnea, and extent of edema, (2) how the patient responded during the preliminary control period, and (3) the opinion of the ward physicians, who made their observations entirely independently.

METHOD OF STUDY

Before digitalization, the maximum effect of absolute rest in bed, the administration of oxygen and sedatives, limitation of fluid intake, and dietary restrictions was ascertained in each case. In seven cases, the preliminary period of observation was omitted because immediate digitalization was considered necessary. Ventricular rates, pulse rates, and blood pressures were recorded daily. At least one electrocardiogram was taken shortly before digitalization began. All patients, with the exception of the two who had recent myocardial infarction, were weighed daily. The weight curve was an excellent guide for following the course of the patient's illness. When the weight remained constant, or when there was an increase in weight during the preliminary control period, rapid digitalization by the combination of ouabain and digitalis leaf was instituted.

When this state had been achieved, 0.5 mg. (5 cat units) of ouabain was given intravenously simultaneously with six or eight cat units of digitalis leaf orally; the amount of the latter depended on the estimated edema-free weight of the patient. No other digitalis was given for twenty-four hours. At the end of this time the patient was placed on a daily maintenance dose of one to two cat units of digitalis leaf by mouth. It is important that only reliable preparations* of ouabain and digitalis be used. Ouabain in solution undergoes deterioration, and, unless a recently standardized preparation is used, the desired immediate effect of a dose which is considered adequate will not be obtained.

Immediately preceding digitalization, ventricular rates, pulse rates, and blood pressures were recorded repeatedly, until constant levels had become established. Ouabain and digitalis were then administered, and the above observations were continued at fifteen-minute intervals for a period of two hours. Electrocardiograms were taken twenty-four hours later, and at frequent intervals thereafter. In five cases, in which auricular fibrillation was present, electrocardiograms were taken at fifteen-minute intervals during the first two-hour period of observations.

All patients were observed daily for symptoms and signs of digitalis toxicity, evidences of improvement, and changes in weight, blood pressure, and ventricular and pulse rates.

Both subjective and objective evidences were used as criteria for improvement. During the first two hours of constant observation, improvement was judged by the general appearance of the patient, decrease in dyspnea, lessening or disappearance of orthopnea, diminution of restlessness and agitation, as shown by drowsiness and the occurrence of sleep, increase in pulse pressure, improvement of the pulse volume,

*Ampules of ouabain, in a concentration of 2.5 cat units per c.c., and tablets of digitalis (whole leaf) of multiple cat unit strength were supplied by Carroll Dunham Smith Pharmacal Company, of Orange, N. J. The potency of these preparations was confirmed in our laboratory by the Hatcher and Brody method of assay.

TABLE I

CARDIAC DIAGNOSIS AND DEGREE OF CONGESTIVE FAILURE

DIAGNOSIS	NUMBER OF CASES	NORMAL RHYTHM	AURICULAR FIBRILLATION	BUNDLE BRANCH BLOCK	MYOCARDIAL INFARCTION	AORTIC INSUFFICIENCY	FAILURE			
							∓	+	++	+++
Arteriosclerotic	17*	16*	1	4	7		4	4	6	3
Hypertensive	10	10		1			2	2	4	2
Arteriosclerotic and Hypertensive	16	13	3	2	1		0	3	10	3
Rheumatic	11	4	7	1		5	1	4	4	2
Syphilitic	3	3				3	2	0	0	1
Rheumatic and Hypertensive	1	1					0	1	0	0
Syphilitic and Hypertensive	1	1				1			1	
Hyperthyroid	1		1				1			
Total	60*	48*	12	8	8	9	10	14	25	11

*One patient treated on two admissions.

TABLE II

RELATION OF TIME OF ONSET OF IMPROVEMENT TO TYPE OF HEART DISEASE

DIAGNOSIS	NO. OF CASES	NUMBER OF PATIENTS IMPROVED IN				
		15 MINUTES	1 HOUR	2 HOURS	24 HOURS	NONE
Arteriosclerotic	17*	3 (17.7%)	6 (35.3%)	3 (17.7%)	5 (29.4%)	
Arteriosclerotic and hypertensive	16	5 (31.2%)	4 (25%)	2 (12.5%)	5 (31.2%)	
Hypertensive	10	5 (50%)	2 (20%)	3 (30%)		
Rheumatic	11	3 (27.2%)	7 (63.6%)	1 (9%)		
Syphilitic	3	1	1	1		
Rheumatic and hypertensive	1					1
Syphilitic and hypertensive	1			1		
Hyperthyroid	1	1				
Total	60*	18 (30%)	20 (33.3%)	11 (18.2%)	10 (16.6%)	1 (1.6%)

*One patient treated on two admissions.

disappearance of gallop rhythm, if it had been present prior to treatment, and, in patients with auricular fibrillation, slowing of the ventricular rate and disappearance of the pulse deficit. Subjective evidence in the absence of objective signs was not considered of major importance. It consisted of the patient's statements with regard to ease in breathing and lessening or disappearance of precordial and epigastric distress. Criteria for improvement at the end of twenty-four hours were the same, and, in addition, consideration was given to decrease in amount of edema, as judged by the weight curve.

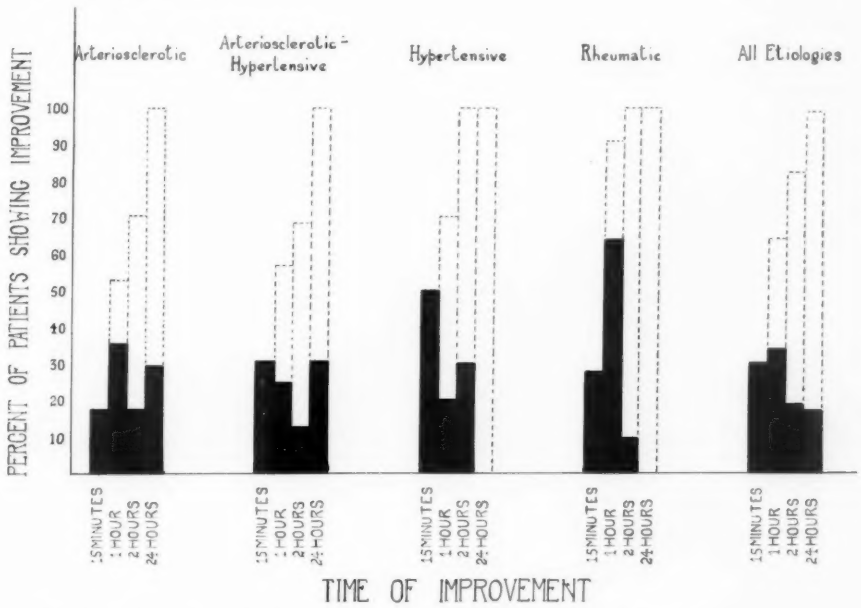

Fig. 2.—Time of onset of improvement in relation to type of heart disease.

RESULTS

In Table II and Fig. 2, the results as to time of onset of improvement in relation to the type of heart disease are summarized. Digitalization was produced sixty times in fifty-nine cases. One patient was treated on two occasions. Improvement was noted within fifteen minutes in eighteen (30 per cent) of the sixty trials, within one hour in thirty-eight (63.3 per cent), and within two hours in forty-nine (81.7 per cent). Improvement, therefore, occurred very rapidly in the majority of the cases. As a rule, this improvement, once established, was progressive, so that the maximum effect of digitalization occurred at twenty-four hours. The only exception was the patient with hyperthyroidism and auricular fibrillation, who, in spite of immediate improvement, with slowing of the ventricular rate from 138 to 90 per minute within one and one-half hours, had lost the effect at the end of twenty-four hours.

It is evident from Table II and Fig. 2 that the type of heart disease determined, to a large extent, the time when improvement first mani-

fested itself. With one exception, all of the rheumatic patients showed improvement within one hour. The early improvement in this group may be explained by the fact that so many of the patients had auricular fibrillation. All patients with hypertension, uncomplicated by arteriosclerosis, were improved within two hours. However, when arteriosclerosis was an etiologic factor in the heart disease, in only approximately 70 per cent of the patients was improvement noted within the first two hours.

TABLE III

RELATION OF TIME OF ONSET OF IMPROVEMENT TO TYPE OF CARDIAC MECHANISM

MECHANISM	NO. OF CASES	NUMBER OF PATIENTS IMPROVED IN				
		15 MINUTES	1 HOUR	2 HOURS	24 HOURS	NONE
Auricular fibrillation	12	3 (25%)	7 (58.3%)	1 (8.3%)	1 (8.3%)	
Normal sinus rhythm	48*	15 (31.2%)	13 (27.1%)	10 (21%)	9 (18.7%)	1 (2.1%)
Total	60*	18 (30%)	20 (33.3%)	11 (18.3%)	10 (16.6%)	1 (1.6%)

*One patient treated on 2 admissions.

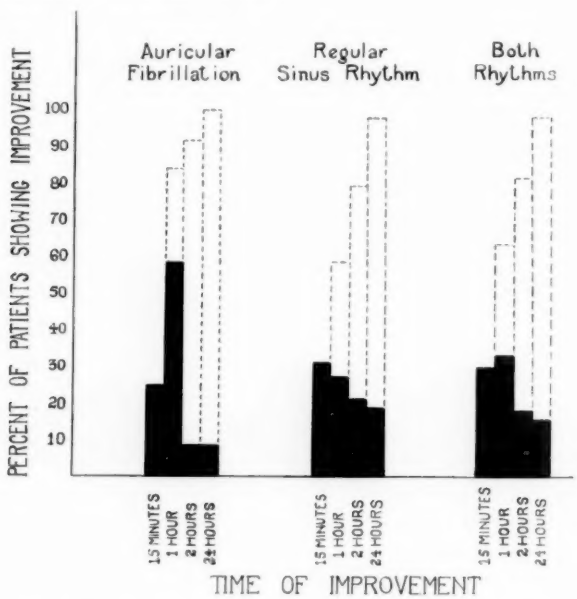

Fig. 3.—Time of onset of improvement in relation to type of cardiac mechanism.

The cardiac mechanism appeared to have some relationship to the time of onset of improvement (see Table III and Fig. 3). Eighty-three per cent of the patients with auricular fibrillation were improved within one hour, whereas only 58 per cent of those with normal sinus rhythm showed improvement in this period.

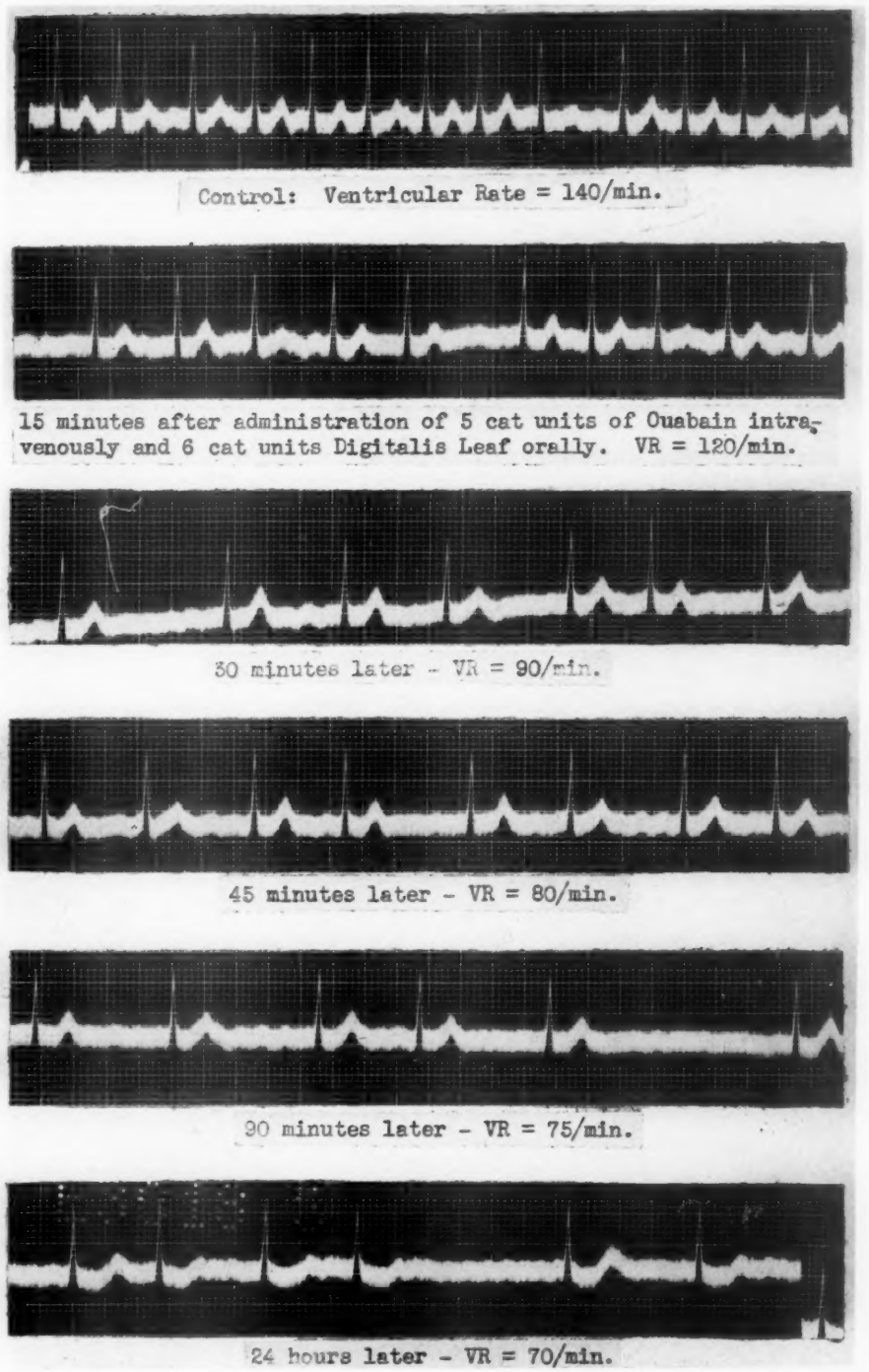
Control: Ventricular Rate = 140/min.
15 minutes after administration of 5 cat units of Ouabain intravenously and 6 cat units Digitalis Leaf orally. VR = 120/min.
30 minutes later - VR = 90/min.
45 minutes later - VR = 80/min.
90 minutes later - VR = 75/min.
24 hours later - VR = 70/min.

Fig. 4.—Electrocardiogram of a patient with auricular fibrillation, following digitalization by means of a combination of oubain and digitalis leaf.

There was no definite correlation between the degree of congestive heart failure and the time of onset of improvement. The age of the patient was not a factor.

A typical response to this method of digitalization is illustrated by the consecutive electrocardiograms of a patient with auricular fibrillation (see Fig. 4). Fifteen minutes after beginning treatment there was a significant reduction in the ventricular rate. Ventricular slowing continued progressively, and the full therapeutic response was achieved within twenty-four hours. This effect was maintained with two cat units of digitalis leaf daily. Fig. 5 illustrates the course of events in a patient with normal sinus rhythm. There was rapid improvement in the patient's appearance. His respiratory difficulty

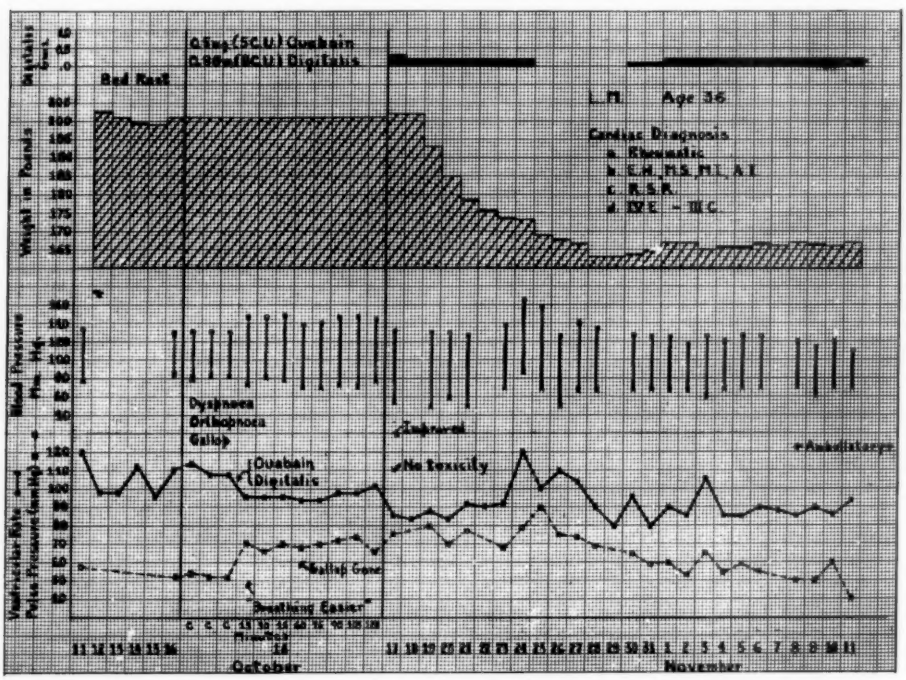

Fig. 5.—Clinical course of patient with normal sinus rhythm, following digitalization by means of a combination of ouabain and digitalis leaf. M. N., aged 42 years, had rheumatic heart disease, mitral stenosis and insufficiency. Weight was 107 pounds. Clinical improvement was shown within fifteen minutes. There was no digitalis toxicity.

decreased, and the pulse pressure rose from 51 to 70 mm. Hg. Within one hour his gallop rhythm disappeared. His condition improved progressively during the following twenty-four hours. A daily maintenance dose of digitalis leaf by mouth caused a rapid loss of edema, as evidenced by the weight curve. Anorexia and nausea occurred on the ninth day of digitalization. Digitalis therapy was discontinued for five days and then reinstituted, and the patient's course thereafter was uneventful.

TOXICITY

Eleven patients (18 per cent) showed evidences of mild toxicity at the end of twenty-four hours (Table IV); six had anorexia, seven, nausea, three, vomiting, and four, prolongation of the P-R interval of the electrocardiogram. Neither abnormal rhythms nor multiple premature systoles were observed. When symptoms of toxicity developed, there was an apparent relationship between the dose of digitalis leaf and the weight of the patient. Of the eight patients who became toxic on 6 cat units of digitalis, six weighed less than 120 pounds. Two of the three patients who received 8 cat units of digitalis leaf weighed less than 150 pounds. It is therefore recommended that, with this method of treatment, the dose of digitalis be regulated in the following manner: For patients who weigh less than 125 pounds, use 4 cat units (0.4 Gm.); for those who weigh between 125 and 175 pounds, 6 cat units (0.6 Gm.); and for those who weigh over 175 pounds, 8 cat units (0.8 Gm.).

COMMENT

The occurrence of mild toxicity in the above cases is indicative of complete digitalization. Evidence that a concentration of digitalis high in the therapeutic range was obtained is furnished by the appearance of mild toxicity in five other cases in which a maintenance dose of two cat units (0.2 Gm.) of digitalis leaf was given for from one to four days.

This method of therapy has the following advantages: (1) the use of ouabain brings about rapid improvement; (2) the simultaneous administration of the more slowly absorbed digitalis leaf not only maintains this improvement, but also decreases or abolishes the gap between the beginning of digitalization and the establishment of a maintenance dose; (3) although more rapid than the usual method of digitalization, this method is a safe one, and is no more likely to produce toxicity; (4) the method is applicable to patients with normal sinus rhythm, as well as those with auricular fibrillation; (5) the technique of administration is relatively easy. Complicated calculations are not necessary to estimate the initial and subsequent doses of digitalis.

SUMMARY

1. A method of obtaining rapid digitalization by the simultaneous administration of ouabain intravenously and digitalis leaf orally is presented.

2. Digitalization was produced sixty times in fifty-nine cases. The patients had varying degrees of congestive heart failure and different types of heart disease; their ages ranged from 28 to 79 years.

TABLE IV

PATIENTS PRESENTING EVIDENCE OF TOXICITY TWENTY-FOUR HOURS AFTER DIGITALIZATION WITH OUABAIN AND DIGITALIS LEAF

PATIENT	AGE	WT.	DIAGNOSIS	RHYTHM	DOSE OF DIG. LEAF	ANOREXIA	NAUSEA	VOMITING	EKG CHANGES
S.D.	28	140	Rheumatic. EH, MS, MI, AI.	AF	8		Y	Y	
M.S.	72	100	Arteriosclerotic. EH, CS, MF.	AF	6	Y	Y		
R.F.	48	105	Rheumatic and Hyper. EH, MI, MS.	RSR	6	Y	Y		P-R interval 0.21 sec.
R.S.	60	110	Hyper. and AS. EH, CS, MF.	RSR	6				P-R interval 0.33 sec.
A.R.	49	140	Rheumatic. EH, MS, MI, AI.	RSR	6	Y			
J.B.	57	107	Hyper. EH, Dil. Aorta.	RSR	6	Y	Y	Y	
D.H.	69	172	Hyper. and AS. EH, CS, MF.	RSR	8	Y	Y		
R.L.	48	150	Arteriosclerotic. EH, CS, MF, Old Myo. Infaret.	RSR	8	Y	Y		
R.P.	65	105	Hyper. and AS. EH, CS, MF.	RSR	6		Y	Y	
M.N.	73	117	Hyper. EH.	RSR	6				P-R interval 0.22 sec.
J.R.	71	145	Arteriosclerosis. EH, CS, MF. Recent Myo. Infarct.	RSR	6				P-R interval 0.24 sec.
TOTAL 11 patients (18.3%)						6	7	3	4

3. In the majority of the cases, improvement occurred within one hour. This improvement, once established, was progressive; the maximum effect was attained at the end of twenty-four hours.

4. After the initial digitalization, it was not difficult to establish the maintenance dose of digitalis leaf.

5. The method was found to be applicable to patients with normal sinus rhythm, as well as to those with auricular fibrillation.

6. Evidences of toxicity were the least that could be expected, indicating that the method is a safe one.

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RHEUMATIC HEART DISEASE

An Analysis of 796 Cases

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THE term "rheumatic heart disease" includes (1) the type of valvulitis and vegetation immediately associated with acute rheumatic fever or chorea, (2) valve deformities resulting from previous attacks of acute rheumatic valvulitis, and (3) the rather unusual condition of adherent pericardium without an associated valvular deformity, or cases in which, even if there is a slight valvular deformity, death results for the most part from the adherent pericardium. Rheumatic infection of the pericardium or myocardium, without valvulitis, is rarely seen.

The verrucous vegetations which are associated with acute rheumatic fever are so characteristic of rheumatic infection that a diagnosis of rheumatic valvulitis can be made without the immediate presence of rheumatic arthritis. These valvular lesions are probably the most common and most characteristic manifestations of rheumatic infection. A few of the cases reported herein as instances of acute or recurrent rheumatic endocarditis are included for anatomic reasons.

Nonsyphilitic valvular deformities resulting in stenosis and insufficiency are caused by previous attacks of rheumatic valvulitis. Proliferative inflammation occurs in the valve. This results in a scar which commonly becomes calcified. Although bacterial valvulitis may bring about an increase in the amount of connective tissue in a valve, healing in clinically typical cases of bacterial endocarditis is so rare that it becomes obvious that healed valve deformities, which are so commonly responsible for cardiac failure in the middle and later decades, are seldom, if ever, the result of bacterial endocarditis.

Atherosclerosis is commonly found in the valves, especially the mitral, but available evidence seems to indicate that atherosclerotic changes in the cusps, although common, are seldom, if ever, severe enough to produce valvular stenosis or insufficiency of a degree sufficient to cause cardiac failure.

If we exclude tuberculous pericarditis, the cardiac failure which is caused by an adherent pericardium appears, in most cases, to be the result of a rheumatic infection. This condition seldom occurs except in association with a rheumatic valvular involvement.

In this paper, the autopsy cases of rheumatic heart disease which were encountered in the Department of Pathology at the University

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of Minnesota during the years 1910-1937 are analyzed in respect to general incidence, incidence of types, etiology, pathology, and pathogenesis; and some important clinical applications are derived from the analysis.

General Incidence.—During the years 1910-1937 there were 27,957 autopsies, of which 4,254 were done on patients with noncongenital cardiac disease (15.2 per cent). In 1,598 (37.6 per cent) of these cases, the disease was infectious in origin (rheumatic; bacterial; syphilitic; toxic myocarditis). There were 796 cases of rheumatic heart disease (Table I). This comprised about 50 per cent of all of the cases of infectious heart disease, and 18.7 per cent of the total number of cases of noncongenital cardiac disease.

TABLE I

TYPES OF RHEUMATIC HEART DISEASE (796 CASES)

1. Acute rheumatic endocarditis (98)		12.31%
2. Recurrent rheumatic endocarditis (76)		9.54
3. Valve deformities (586)		73.61
a. Incompletely healed (113)	19.28%	
b. Completely healed (239)	40.78	
c. Calcified, nodular, aortic (234)	39.93	
4. Adherent pericardium (36)		4.52

Incidence of Types.—The cases of rheumatic heart disease (Table I) were divided into four groups: acute rheumatic endocarditis, ninety-eight cases (12.31 per cent); recurrent rheumatic endocarditis, seventy-six cases (9.54 per cent); valve deformities, 586 cases (73.6 per cent), and adherent pericardium, thirty-six cases (4.52 per cent). The first was characterized by the fact that there were verrucous vegetations on valves which, by gross examination, appeared not to have been previously thickened. Upon microscopic examination, however, some of the valves in this group were found to have such well-developed blood vessels that the possibility of a previous infection was suggested. The dividing line between acute rheumatic and recurrent rheumatic endocarditis is not sharp.

The second group, comprising cases of recurrent rheumatic endocarditis, was similar to the first, except that the vegetations were on grossly thickened fibrous valves. In many cases there was a history of repeated attacks of rheumatic fever.

In the third group, made up of cases of healed valve deformities, there were thickened, scarred, and, frequently, calcified valves. In some instances, evidences of lack of complete healing could be detected, especially microscopically.

This third group of cases of rheumatic heart disease was further divided into three subgroups: (a) incompletely healed valves, 113 cases (19.28 per cent); (b) completely healed valves, 239 cases (40.78 per cent); and (c) calcified, nodular aortic valves, 234 cases (39.93

per cent). The last subgroup was studied separately, for it is thought by some that this lesion results from a metabolic disturbance or atherosclerosis, rather than rheumatic infection, and because it is a fairly definite clinical entity. A study of this type of valve deformity has already been reported.[1] Evidence definitely favors the theory of rheumatic origin of this lesion. There appears to be no more evidence that the aortic valvular deformity, with calcification, is nonrheumatic in origin than that the calcific mitral valvular deformity is not the result of rheumatic infection. Calcification of the scarred valve is as common in the mitral valve as in the aortic. In fact, there are few extensively scarred valves which are not calcified to a greater or less degree. If all of the calcific aortic valvular deformities were regarded as nonrheumatic in origin, it would have to be concluded that the aortic valve is not commonly attacked by the rheumatic infectious agent. At least 85 per cent of deformed aortic valves are calcified.

The fourth group, comprising cases of rheumatic heart disease in which death appeared to have been caused primarily by an adherent pericardium, was small (thirty-six cases, or 4.52 per cent). In more than half of these, slight valvular deformities were present also. In only fifteen of the thirty-six cases were the valves normal grossly. Death purely as a result of adherent pericardium is rare.

Etiology.—The etiology of acute rheumatic fever and rheumatic heart disease is considered in this paper in detail only in so far as information can be obtained from those cases in which an autopsy was performed. Age and sex are discussed as etiologic factors.

It is generally believed that acute rheumatic fever is an infectious disease. There is no general agreement concerning the nature of the infectious agent. The three theories are (1) that it is caused by an unknown infectious agent; (2) that it is caused by the *Streptococcus hemolyticus* or *viridans;* and (3) that it is a virus infection. The first theory is based primarily on the belief that the rheumatic inflammation is of a specific type. The material which forms the basis of this report furnishes some information on this point, and this will be considered further under the discussion of rheumatic inflammation. The *Streptococcus viridans* is the organism which has been most commonly isolated from the blood, joints, and pericardial exudates of patients with acute rheumatic fever. This occurred in many of the cases of acute and recurrent rheumatic endocarditis in this series. These streptococci are regarded by some as secondary invaders, but the relatively high percentage of positive cultures from previously healthy persons who became ill rather suddenly with acute rheumatic fever does not strongly support this. Streptococcic allergy is generally considered, by those who believe in the streptococcic theory, to be a conspicuous factor in the pathogenesis of rheumatic inflammation. The virus theory is based primarily upon the observations of Schlesinger, et al.[2] They found

bodies in the pericardial exudate which resembled the elementary bodies of a virus. Recently, Sabin[3] has isolated filtrable pleuropneumonia-like organisms from mice. These organisms, when injected into other mice, were capable of producing arthritis in a high percentage of cases. Swift[4] has isolated a similar organism from rheumatic patients. There is nothing about the type of inflammation in rheumatic heart disease which definitely favors or disfavors the theory that a virus is the active agent in rheumatic infection. The type of cellular reaction which occurs in rheumatic inflammation can be simulated closely experimentally by injecting rabbits, especially those which are allergic, with streptococci.

The age and sex incidence in the cases of acute rheumatic endocarditis is shown in Table II. Death occurred early in this group; 71.4 per

TABLE II

AGE AND SEX INCIDENCE OF ACUTE AND RECURRENT RHEUMATIC ENDOCARDITIS (174 CASES)

DECADE	ACUTE RHEUMATIC (98 CASES)						RECURRENT RHEUMATIC (76 CASES)					
	MALES 49		FEMALES 49		TOTAL		MALES 38		FEMALES 38		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	15	30.6	16	32.6	31	31.6	0	0	3	7.9	3	3.9
2	17	34.7	15	30.6	32	32.6	7	18.4	12	31.6	19	25.0
3	3	6.1	9	18.4	12	12.2	7	18.4	5	13.2	12	15.8
4	4	8.2	4	8.2	8	8.2	9	23.7	4	10.5	13	17.1
5	2	4.1	1	2.0	3	3.1	6	15.8	9	23.7	15	19.7
6	3	6.1	0	0	3	3.1	6	15.8	4	10.5	10	13.2
7	3	6.1	1	2.0	4	4.1	2	5.2	0	0	2	2.6
8	1	2.0	0	0	1	1.0	1	2.6	1	2.6	2	2.6
9	1	2.0	2	4.1	3	3.1	0	0	0	0	0	0
10	0	0	1	2.0	1	1.0	0	0	0	0	0	0
Total	49	99.9	49	99.9	98	100.0	38	99.9	38	100.0	76	99.9

cent of the males and 81.6 per cent of the females, or a total of 76.4 per cent, died in the first three decades. There were forty-nine males and forty-nine females.

Of the seventy-six patients who had recurrent rheumatic endocarditis (Table II), the greatest percentage of males (23.7 per cent) died in the fourth decade, and the greatest percentage of females (31.6 per cent) in the second decade; 90.8 per cent of the total number died in the second to sixth decades, inclusive. Death occurred at a later stage than in the acute rheumatic group. The number of males and females was the same, thirty-eight each. It is probable that more females than males died with recurrent rheumatic endocarditis, for in the later decades the number of males in our series is about twice the number of females.

The age and sex incidence of the valve deformities in subgroups "a" and "b," of group III, is shown in Table III. There were 352 cases, 179 in males and 173 in females. By correcting for the fact that twice as many males as females come to autopsy in most of the decades of this group, there would be nearly twice as many females in these two

groups. This greater number of females is probably accounted for by the fact that patients with aortic lesions were taken from these groups and placed in subgroup "c."

The highest death rate for both sexes in subgroups "a" and "b" occurred in the fifth decade; 90.6 per cent of the total number in the two groups died between the third and seventh decades, inclusive. Death from these valve deformities occurred, as a rule, later in life than among the patients with acute or recurrent rheumatic infection.

In subgroup "c" (calcified, nodular, aortic valvular deformity) there was a decided preponderance of males (males 197 and females 97) (Table III). Death occurred later in subgroup "c" than in subgroups "a" and "b." The greatest percentage of patients of both sexes in subgroup "c" died in the sixth decade; 90.2 per cent of the total number died between the fourth and eighth decades. The reason for the greater average length of life in this group is the fact that the chief lesion was of the aortic valve, for, as was shown in a previous publication,[5] a patient with an aortic lesion will live, on an average, from fifteen to twenty years longer than one with a mitral deformity.

TABLE III

AGE AND SEX INCIDENCE IN CASES OF VALVULAR DEFORMITIES (586 CASES)

DECADE	SUBGROUPS "A" AND "B" (352)						SUBGROUP "C" (234)					
	MALES		FEMALES		TOTAL		MALES		FEMALES		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	1	0.6	3	1.7	4	1.1	0	0	0	0	0	0
2	2	1.1	4	2.3	6	1.7	2	1.0	1	2.7	3	1.3
3	22	12.3	19	11.0	41	11.7	7	3.6	3	8.1	10	4.3
4	38	21.2	35	20.2	73	20.8	24	12.1	3	8.1	27	11.5
5	62	34.6	45	26.0	107	30.3	35	17.8	5	13.5	40	17.1
6	32	17.9	35	20.2	67	19.0	46	23.4	9	24.3	55	23.6
7	11	6.1	20	11.6	31	8.8	43	21.8	5	13.5	48	20.5
8	8	4.5	10	5.8	18	5.1	36	18.2	5	13.5	41	17.5
9	3	1.7	2	1.2	5	1.4	4	2.0	5	13.5	9	3.8
10	0	0	0	0	0	0	0	0	1	2.7	1	0.4
Total	179	100.0	173	100.0	352	99.9	197	99.9	37	99.9	234	100.0

Of the thirty-six patients who died from the effects of an adherent pericardium, twenty-seven were males and nine were females. The death rate was highest among the males in the second and third decades, and, among the females, in the second, fourth, and fifth decades.

There were 490 males and 306 females in this series of 796 cases of rheumatic heart disease. This does not approximate the relative sex incidence of rheumatic heart disease in the general population, for, from the third decade upward, there were twice as many males as females in the autopsy material.

To obtain, approximately, the relative incidence of rheumatic heart disease in males and females, the number of male or female patients who had any of the types of rheumatic heart disease was compared with the total number of males or females who came to autopsy (Table

IV). There were 18,227 autopsies on males, and 9,730 on females. This gave a percentage, in males, of 2.688, and, in females, of 3.144 of patients with rheumatic heart disease. When expressed as the number of cases of rheumatic heart disease per thousand autopsies, there were about twenty-seven males, and thirty-one females, respectively, per thousand.

It cannot be said definitely that this sex ratio holds in the general population, for there may be some degree of selection of cases in an autopsy service; however, the autopsy material at the University of Minnesota is fairly well distributed. It comes from several public and private hospitals, from the coroner's service, and from physicians in private practice. Furthermore, the percentage of autopsies obtained in most of the hospitals is high. In the city of Minneapolis it is about 15 per cent. It seems fair to conclude that rheumatic heart disease occurs with about the same frequency in the two sexes.

Pathology and Pathogenesis.—The pathologic changes in the valves and endocardium, the myocardium, the coronary arteries, and the pericardium were studied.

The valves which are involved in rheumatic heart disease are primarily the aortic and mitral, but the tricuspid and pulmonic valves are not infrequently infected, especially when the disease is acute, and generally in association with involvement of the aortic or mitral valves, or both. In the ninety-eight cases of acute rheumatic endocarditis (Table V),

TABLE IV

SEX INCIDENCE OF THE DIFFERENT KINDS OF RHEUMATIC HEART DISEASE IN THE ENTIRE AUTOPSY SERIES (18,227 MALES AND 9,730 FEMALES)

	MALES			FEMALES		
	NO. AUTOPSIES	NO.	%	NO. AUTOPSIES	NO.	%
Acute rheumatic	18,227	49	0.268	9,730	49	0.503
Recurrent rheumatic	18,227	38	0.208	9,730	38	0.390
Valve deformity Subgroups "a" and "b"	18,227	179	0.982	9,730	173	1.778
Valve deformity Subgroup "c"	18,227	197	1.080	9,730	37	0.380
Adherent pericardium	18,227	27	0.148	9,730	9	0.092
Total	18,227	490	2.688	9,730	306	3.144

the aortic valve was involved alone twice, the mitral valve alone forty-three times, both the aortic and mitral twenty-four times, the tricuspid and mitral nine times, and the tricuspid, aortic, and mitral ten times; there were no cases of involvement of the tricuspid alone, of the tricuspid and aortic, or of the tricuspid and pulmonic. The tricuspid valve was affected, in all, twenty-eight times. The pulmonic valve was involved but once, and, in this case, it was the only valve affected.

Of the seventy-six cases of recurrent rheumatic endocarditis (Table V), the aortic valve alone was infected in but two cases, the mitral

TABLE V

COMBINATIONS OF VALVE INVOLVEMENT IN RHEUMATIC HEART DISEASE (780 CASES)

	A	M	T	P	AM	AT	AP	AMT	AMP	AMTP	MT	MTP	TP	TOTAL
Acute rheumatic	2	43	0	1	24	0	0	10	0	9	9	0	0	98
Recurrent rheumatic	2	21	0	0	30	1	0	11	1	4	6	0	0	76
Valve deformities														
Subgroup "a"	4	65	0	0	28	0	0	8	0	1	7	0	0	113
Subgroup "b"	17	149	0	1	45	0	0	17	0	0	9	0	0	238
Subgroup "c"	136	0	0	0	92	1	0	5	0	0	0	0	0	234
Adherent pericardium	6	11	0	0	2	0	0	1	0	0	0	0	0	20
Total	167	289	0	2	221	2	0	52	1	14	31	0	0	779

valve alone in twenty-one, and the aortic and mitral, together, in thirty. Involvement of the tricuspid alone did not occur. Tricuspid and aortic involvement was noted once, tricuspid and mitral six times, tricuspid, aortic, and mitral eleven times, and tricuspid, pulmonic, aortic, and mitral, four times. In all, the tricuspid was involved twenty-two times, always in combination with involvement of one or more of the other valves. The pulmonic valve was affected four times only, and always in combination with involvement of the aortic, mitral, and tricuspid valves.

Of the 113 cases of subgroup "a" of the valve deformities (Table V), the aortic valve was deformed alone in four, the mitral valve alone in sixty-five, and the aortic and mitral, together, in twenty-eight.

In the 239 cases of subgroup "b" of the valve deformities (Table V), involvement of the aortic valve alone was noted seventeen times, of the mitral alone 149 times, and of the aortic and mitral, together, forty-five times. In the third subgroup of healed valve deformities, comprising calcified, nodular, aortic lesions (234 cases), there was naturally a high incidence of involvement of the aortic valve, for it was upon the character of this valve deformity that this classification was made. The aortic valve alone showed deformity in 136 cases, and both the aortic and mitral in ninety-seven (Table V).

It is possible, and even probable, that the tricuspid and pulmonic valves may have been infected and slightly thickened in any of the cases of valve deformity, but the degree was not marked. A slight degree of valvular deformity cannot be recognized as easily by gross examination as the verrucous vegetations in the cases of acute and recurrent rheumatic endocarditis.

The valves of the left side of the heart showed the greatest incidence of involvement (Table V). Of the 780 cases of rheumatic heart disease in which the valves were affected, there was involvement of the aortic, mitral, or both, in 779 (99.8 per cent). In forty-four (5.6 per cent), the valves on the right side of the heart were affected, and, in all of these except one (pulmonic alone), there was an associated aortic or mitral involvement.

The relation of sex to the three kinds of valvular involvement (aortic alone, mitral alone, and both aortic and mitral) is apparently significant, and may offer an explanation for the high incidence of the calcified, nodular, aortic valvular deformity (subgroup "c") in men who die, as a rule, in the later decades.

In discussing varieties of valvular involvement, three terms are used, namely, aortic alone, mitral alone, and aortic and mitral combined. Any of these may be associated with tricuspid or pulmonic disease. The term "aortic alone" is used to mean that there is no mitral involvement, and "mitral alone" that there is no associated aortic lesion.

TABLE VI

PERCENTAGE OF CASES IN WHICH DEATH WAS CAUSED BY RHEUMATIC HEART DISEASE OR BACTERIAL ENDOCARDITIS, WITH THE FOLLOWING VALVULAR INVOLVEMENT: AORTIC, MITRAL, AORTIC AND MITRAL COMBINED (778 RHEUMATIC CASES AND 455 CASES OF BACTERIAL ENDOCARDITIS; TOTAL 1,233 CASES)

MALES, 18,227 AUTOPSIES								
	A		M		AM		TOTAL	
Acute and recurrent rheumatic	5	0.027	38	0.208	43	0.235	86	0.471
Valve deformity, "a" and "b," and adherent pericardium	21	0.115	110	0.603	64	0.351	195	1.069
Valve deformity "c"	122	0.669	0	0	75	0.410	197	1.080
Total rheumatic, 778; males, 478; females, 300	148	0.811	148	0.811	182	0.998	478	2.622
Bacterial, 455; males, 282; females, 173	75	0.411	103	0.565	104	0.570	282	1.547
Total valvular, 1,233	223	1.223	251	1.377	292	1.602	760	4.169
FEMALES, 9,730 AUTOPSIES								
	A		M		AM		TOTAL	
Acute and recurrent rheumatic	0	0	50	0.513	37	0.380	87	0.894
Valve deformity, "a" and "b," and adherent pericardium	7	0.071	132	1.356	37	0.380	176	1.808
Valve deformity "c"	15	0.154	0	0	22	0.226	37	0.380
Total rheumatic, 778; males, 478; females, 300	22	0.226	182	1.870	96	0.986	300	3.083
Bacterial, 455; males, 282; females, 173	25	0.256	105	1.079	43	0.441	173	1.778
Total valvular, 1,233	47	0.483	287	2.949	139	1.428	473	4.861

There were 478 males and 300 females in the series of 778 cases of rheumatic heart disease in which one of the forms of valvular involvement (aortic alone, mitral alone, or aortic and mitral combined) was present. In Table VI they are placed in three groups: (1) cases of acute and recurrent rheumatic endocarditis; (2) cases of incompletely and completely healed valvular deformities, and cases of adherent pericardium with a valvular deformity, also; and (3) cases in which there was a calcified, nodular, aortic lesion. It is important to note that the percentage of deaths caused by aortic valvular involvement alone was greater, and increased more rapidly, from group 1 to group 3 among the males than among the females. Group 3 included older persons. The mitral alone among the females showed about the same proportional increase, except that there was no mitral alone involvement. The total percentages of combined aortic and mitral involvement were about the same in the two sexes. Among the males the percentage increased from 0.235 in the first group to 0.410 in the third. Among the females the percentage was 0.380 in each of the first 2 groups, but less (0.226) in the third group. As shown in the total rheumatic column, the percentages of aortic alone, mitral alone, and aortic and mitral combined among the males, and aortic and mitral combined among the females, were approximately the same (0.811, 0.811, 0.998, and 0.986, respectively). The incidence of aortic and mitral involvement

among the males was the same. Mitral involvement among the females was 8.274 times as common as aortic. The outstanding differences in percentages were in the incidence of aortic alone and mitral alone among the females. The aortic alone was less, and the mitral alone was greater among the females than the males. It is obvious that females are much more likely to have infection in the mitral valve than in the aortic. This selective valvular involvement was also noted in the 455 cases of bacterial endocarditis (Table VI). The reason for it is not understood.

The gross appearance of the diseased valves presented several interesting features. In acute and recurrent rheumatic valvulitis the vegetations were always on the ventricular surfaces, a short distance from the free margins, of the aortic and pulmonic cusps, and on the auricular surfaces, also a short distance from the free margins, of the mitral and tricuspid cusps. The fact that these surfaces of the valves contain the spongiosa layer, and that there are more vessels in this layer than in the fibrosa on the opposite side of the cusps supports the embolic theory of the pathogenesis of acute rheumatic endocarditis.

The thickening and scarring of the valves, as was shown in a previous paper, are caused by cellular proliferation, which results in an increase of connective tissue within the valve. There is no organization of a thrombus. In rheumatic valvulitis very little thrombus is formed, and what there is contains little or no fibrin. The chordae tendineae are also involved, with resultant thickening and shortening. The scars in all of the valves show a great tendency to undergo calcification, and it is not uncommon to find areas of ossification.

That normal valves have vessels is affirmed by some[6] and denied by others.[7] Those who deny that they exist believe that when vessels are present the valve has previously been inflamed, and that this inflammation has resulted in the development of vessels. The evidence obtained by injecting the coronary arteries and by microscopic examination of the valves seems to favor the belief that normal valves have small vessels which rapidly become congested and enlarged during inflammation.

Microscopically, vessels are easily seen in the inflamed valves early in the course of acute rheumatic valvulitis and acute bacterial endocarditis. These vessels may or may not extend from the point of the vegetation to the ring. Some of the vessels may be seen communicating with indentations on the free surface of the valve, which suggests that they may open through the endothelium of the valve; this occurs in the heart, and, as Winternitz, et al.,[8] have shown, also in the arteries. It seems evident from the association of an increase in vessels and proliferative and exudative inflammation in the ring that, in most cases, the infectious agent probably enters the valve, by way of the coronary vessels, through the ring, but, in not a few instances, an early inflam-

mation, with increased formation of vessels, is seen near the distal part of the cusp, without any evidence of involvement of the proximal part of the valve and the ring. This suggests the possibility that a valve may become infected directly from the blood stream. More work will have to be done before the pathogenesis of acute rheumatic valvulitis can be fully understood.

Microscopically, the inflammation is primarily proliferative. There are large cells with dark-staining nuclei. Others have large, vesicular nuclei. Some of the cells are multinucleated. They resemble the cells which are found in the Aschoff nodules in the myocardium and in rheumatic subcutaneous nodules. A hyaline substance, designated as fibrinoid material by Klinge,[9] and degenerated collagen by Gross and Ehrlich,[10] is also noted. This appears early in the course of the reaction. The inflammation is generally confined to the valves, but the endothelium may break and a platelet thrombus form; this thrombus bears a close resemblance to that which occurs in bacterial endocarditis, except that the latter is larger and contains bacterial colonies.

When the inflammation subsides the nuclei become smaller and a scar remains. Recurrences are common. The end result is a healed deformity of the valve. Evidences of previous inflammation are as common in the calcified, nodular, aortic type as in other forms of healed valvular deformities. The processes which lead to scarring of the mitral and aortic valves appear to be similar.

The *endocardium* of the auricles, as was pointed out by MacCallum,[11] and later confirmed by our observations, is affected in acute rheumatic endocarditis with about the same frequency (40 per cent) as in subacute bacterial endocarditis. There were no rheumatic vegetations on the ventricular endocardium, except on the chordae tendineae, in our cases of acute rheumatic endocarditis.

The chief gross change noted in the *myocardium* was hypertrophy, and the criterion of hypertrophy was an increase in the weight of the heart. This increase in weight was common in cases of acute and recurrent rheumatic endocarditis, but the degree of increase was not ascertained as accurately as in the cases of healed valve deformity, for there was a greater variation in age, and the presence of fibrinous pericarditis made it difficult to obtain the exact weight of the myocardium. The cause of the hypertrophy seems to have been valvular insufficiency.

When the heart weighed 500 grams, or more, in males, and 450 grams, or more, in females, it was regarded as definitely hypertrophied. A weight of 400 to 499 grams, in males, and 350 to 449 grams, in females, was taken to indicate that hypertrophy was probably present, especially in the upper brackets. Weights below 400 grams, in males, and 350 grams, in females, were considered normal; if any of these hearts came from small persons, they may have been slightly hypertrophied. The

foregoing estimates, although they do not take into account the relation of body weight to heart weight in each individual case, agree well with the observations of Smith,[12] in his comparison of body weights and heart weights. His maximum, average, normal heart weight for a male weighing 200 pounds was 412 grams, and, for a woman weighing 195 pounds, 371 grams. The possibilities of error in our estimations of hypertrophy are obviously on the side of passing slightly hypertrophied hearts as normal. This was not regarded as serious in our series, for, inasmuch as many different pathologists performed the autopsies, there was bound to be a variation in the amount of aorta left attached to the heart. Many of the hearts were weighed on spring balances, which might introduce another error.

The heart weights in 339 of the 352 cases in subgroups "a" and "b," of group III (healed and unhealed valve deformities), are shown

TABLE VII

DEGREE OF HYPERTROPHY IN CASES OF RHEUMATIC VALVE DEFORMITIES AND ADHERENT PERICARDIUM

CODE OF WEIGHTS OF HEARTS

1. MALES BELOW 400 GRAMS, FEMALES BELOW 350 GRAMS
2. MALES 400-499, FEMALES 350-449
3. MALES 500-799, FEMALES 450-749
4. MALES 800 OR MORE, FEMALES 750 OR MORE

	VALVE DEFORMITIES SUBGROUPS "A" AND "B" (339)						VALVE DEFORMITIES SUBGROUP "C" (234)					
	MALES		FEMALES		TOTAL		MALES		FEMALES		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	24	14.1	26	15.4	50	14.7	4	2.0	2	5.4	6	2.6
2	34	20.0	66	39.0	100	29.5	27	13.7	11	29.7	38	16.2
3	102	60.0	75	44.4	177	52.2	135	68.5	24	64.9	159	68.0
4	10	5.8	2	1.2	12	3.5	31	15.7	0	0	31	13.2
	170	99.9	169	100.0	339	99.9	197	99.9	37	100.0	234	100.0
	ADHERENT PERICARDIUM (26)						TOTAL 599					
	MALES		FEMALES		TOTAL		MALES		FEMALES		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	3	15.0	0	0	3	11.5	31		28		59	9.8
2	2	10.0	2	33.3	4	15.4	63		79		142	23.7
3	5	25.0	2	33.3	7	26.9	242		101		343	57.3
4	10	50.0	2	33.3	12	46.1	51		4		55	9.2
	20	100.0	6	99.9	26	99.9	387		212		599	100.0

in Table VII. The weights were not recorded in all of the 352 cases In twenty-four males (14.1 per cent) and twenty-six females (15.4 per cent), a total of fifty (14.7 per cent), the hearts were not hypertrophied. Fifteen of the twenty-four males and twenty-one of the twenty-six females had mitral lesions only. In the group with doubtful hypertrophy there were thirty-four males (20 per cent) and sixty-six females (39 per cent), a total of 100 (29.5 per cent). Unquestionable, but not extensive, hypertrophy was present in 102 (60 per cent) of the males and seventy-five (44.4 per cent) of the females, a total of

177 (52.2 per cent). In all but fifty (14.7 per cent) of these 339 cases of valve deformities there was some degree of cardiac hypertrophy. The hearts of only ten males and two females (3.5 per cent) showed extensive hypertrophy (800 grams, or more, in males, and 750 grams, or more, in females). Of the 339 cases, there were mitral lesions in all but twenty; there were aortic lesions in 120, and, in twenty, aortic lesions only. Fifteen of the twenty-four males with heart weights below 400 grams, and twenty-one of the twenty-six females with heart weights below 350 grams, had mitral lesions only. With a preponderance of mitral deformities, especially when the deformity is stenosis, excessive hypertrophy is not common.

Hypertrophy was more common in the cases of calcified, nodular, aortic deformity (Table VII). There were 234 cases. Only four males (2 per cent) and two females (5.4 per cent), a total of six (2.6 per cent), had no hypertrophy. Cases of doubtful hypertrophy were also fewer than in the other groups of valve deformities; there were twenty-seven males (13.7 per cent), and eleven females (27.7 per cent), a total of thirty-eight (16.2 per cent). The percentage of females with doubtful hypertrophy, or none at all, was greater than that of the males. The number with definite, but not extensive, hypertrophy was high in this group; there were 135 males (68.5 per cent) and twenty-four females (64.9 per cent), a total of 159 (68 per cent). Excessive hypertrophy was also more common in this group. Thirty-one males (15.7 per cent) had hearts weighing 800 grams, or more. None of the females had excessive hypertrophy, amounting to 750 grams, or more. All members of this group had aortic valve deformities, and ninety-seven had a mitral deformity, also. Twenty-two of the ninety-seven with a mitral deformity were females.

The degree of cardiac hypertrophy in cases in which cardiac failure had been caused entirely or primarily by an adherent pericardium is shown in Table VII. Of the thirty-six cases, only twenty-six were considered. In some of the remaining ten cases the patient had been too young, or the weight of the heart was not recorded. There were twenty males and six females. Three of the males had hearts weighing less than 400 grams. None of the female hearts weighed less than 350 grams. Two males had hearts which weighed between 450 and 499 grams. Two female hearts weighed between 350 and 449 grams. Fifteen males had hearts weighing 500 grams, or more; ten weighed 800 grams, or more; the heaviest weighed 1,350 grams. Of course, in all of these cases a small part of the weight was contributed by the adherent pericardium. Four female hearts weighed from 450 grams to 750 grams; the heaviest weighed 750 grams.

Of the total of 599 hearts, only fifty-nine (9.8 per cent) failed to show some degree of hypertrophy. Cardiac hypertrophy is a common pathologic change in rheumatic heart disease, especially in cases in

which death results from healed valve deformities. The hypertrophy appears to be caused by increased work. The greatest degree of hypertrophy was found in the hearts which were the seat of an aortic valvular deformity, and when an adherent pericardium had been the chief cause of death.

Gross areas of fibrosis in the myocardium were seen only occasionally, and then with difficulty.

Microscopic examination of the myocardium revealed Aschoff nodules; diffuse inflammation, with a cellular reaction similar to that in the Aschoff nodules; abscesses; and periarterial scars which were partly or completely healed. A diffuse suppurative myocarditis was seldom observed.

The incidence of the different kinds of inflammation of the myocardium was ascertained by examining five sections from each heart. Sections of moderate size were taken from the apex and two other areas of the left ventricle, from the septum, and from the base of the right ventricle. Sometimes more sections were examined. Table VIII

TABLE VIII

EVIDENCE OF MYOCARDITIS IN RHEUMATIC HEART DISEASE (295)

	ASCHOFF NODULES		DIFFUSE INFLAMMATION		ABSCESSES		PERIARTERIAL SCARS		ONE OR MORE	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Acute rheumatic (67)	45	67.16	12	17.91	2	2.98	21	31.34	53	79.10
Recurrent rheumatic (53)	30	56.60	3	5.66	0	0	30	56.60	40	75.47
Valve deformity subgroup "a" (43)	7	16.27	3	6.97	0	0	24	55.81	25	58.13
Valve deformity subgroup "b" (65)	9	13.84	8	12.30	1	1.53	24	36.92	25	38.46
Valve deformity subgroup "c" (67)	7	10.44	4	5.97	0	0	32	47.76	33	49.25

gives the frequency of the various microscopic pathologic changes which were noted in the myocardium in 295 cases of rheumatic heart disease. There were sixty-seven cases of acute rheumatic endocarditis, fifty-three of recurrent rheumatic endocarditis, forty-three of incompletely healed valvular deformities, sixty-five of completely healed valvular deformities, and sixty-seven of calcified, nodular, aortic valve deformity.

The incidence of Aschoff nodules decreased from 67.1 per cent in the acute rheumatic group to 10.4 per cent in the calcified, nodular, aortic group. It was interesting to note that, as the activity of the inflammation decreased, the number of Aschoff nodules diminished, and that the incidence of Aschoff nodules in the two groups of completely healed valvular deformities was nearly the same.

A diffuse, proliferative inflammation was also most common in the acute rheumatic group, but did not decrease as regularly as the Aschoff nodules.

Abscesses were rare. They were seen in only two cases (2.98 per cent) in the acute rheumatic group, and in one (1.53 per cent) of the cases of completely healed valvular deformity.

The periarterial scars differ from those which occur in cases of coronary sclerosis. The former are immediately around the blood vessels, and may be seen in various stages, from degenerating Aschoff nodules and irregular proliferative inflammation, to a completely healed scar. The scar caused by coronary sclerosis is seldom near the vessel.

Periarterial scars were least common in the acute rheumatic group (31.3 per cent), and most numerous in the recurrent rheumatic group (56.6 per cent), but the incidence in the healed rheumatic groups was almost as great. The total incidence of one or more of the above microscopic changes was greatest in the acute rheumatic group (79.1 per cent). It was practically as large in the recurrent rheumatic group (75.4 per cent). In subgroups "a" and "b," of the valve deformities, it was 46.3 per cent, and, in subgroup "c," 49.2 per cent. This was significant in considering the etiology of the three groups of valvular deformities.

Another gross pathologic condition which was noted in rheumatic heart disease was pericarditis. Clinically, the occurrence of pericarditis is often used to help differentiate acute rheumatic endocarditis from bacterial endocarditis.

TABLE IX

INCIDENCE OF PERICARDITIS IN RHEUMATIC HEART DISEASE AND IN BACTERIAL ENDOCARDITIS

I. Rheumatic	
1. Acute rheumatic endocarditis	52.5
2. Recurrent rheumatic endocarditis	41.1
3. Valve deformities	17.0
Subgroup "a"	12.5
Subgroup "b"	22.2
Subgroup "c"	14.1
4. Adherent pericardium	100.0
II. Bacterial endocarditis	17.8

Table IX shows the incidence of pericarditis, either acute or in the stage of adherent pericardium, in the different groups of cases of rheumatic heart disease, and also in the cases of bacterial endocarditis. It is obvious that in the cases of rheumatic valvular deformity there had been an acute rheumatic endocarditis. It is probably fair to assume that, in the cases of old valve deformities in which there was no acute pericarditis or an adherent pericardium, there had never been an acute pericarditis, for the type of pericarditis which is associated with acute rheumatic fever (fibrinous, mainly) undergoes organization early in its course, and fibrous adhesions result. The highest incidence of peri-

cardial involvement, not including the group in which death was caused by adherent pericardium, occurred in the acute and recurrent rheumatic groups, in which it was 52.5 per cent and 41.1 per cent, respectively. In the three subgroups of valvular deformities it was 12.5 per cent, 22.2 per cent, and 14.1 per cent, respectively. Obviously, all of the patients in these three subgroups had passed through an acute stage of rheumatic endocarditis. Therefore, the incidence of pericardial involvement in these groups probably represented the clinical incidence of pericarditis better than that in the two groups in which death occurred during an attack of acute rheumatic endocarditis.

The incidence of pericarditis (17.8 per cent) in the cases of bacterial endocarditis was about the same as the average in the cases of rheumatic valvular deformities, not including the group in which death was caused by an adherent pericardium. Since the incidence of pericardial involvement in the cases of valvular deformities probably represents closely the actual clinical incidence of pericarditis in association with acute rheumatic endocarditis, and since it is nearly the same as the incidence of pericarditis in cases of bacterial endocarditis, it appears obvious that the existence of pericarditis cannot be used clinically to differentiate acute rheumatic endocarditis from bacterial endocarditis.

In not all of the cases of rheumatic heart disease was there evidence of pericarditis. The same can be said of myocarditis. The term pancarditis, although generally applicable, cannot always be used, even in autopsy cases of acute rheumatic endocarditis, and certainly less frequently clinically in cases of rheumatic heart disease.

The coronary arteries.—The degree of atherosclerosis of the coronary arteries was studied with interest, for, if the coronary arteries are involved extensively in rheumatic heart disease, a causal relation between the infection and atherosclerosis might be suspected. The degrees of coronary sclerosis mentioned in the autopsy protocols were graded from + to ++++, as nearly as possible. Grade ++++ indicated that the vessels were completely, or almost entirely, closed. A + degree represented a slight amount of sclerosis. The degrees ++ and +++ were intermediate. No sclerosis was recorded as 0.

The condition of the left and right coronary arteries, mainly the descending branches, was described. Table X shows the degree of sclerosis in the different groups of cases of rheumatic heart disease (acute rheumatic, recurrent rheumatic, healed valve deformities, subgroups "a," "b," and "c," and adherent pericardium, respectively). Of the 796 cases, in only 601 were the coronary arteries sufficiently well described to be rated. In only ten of these was the sclerosis graded ++++, as follows: three, left ++++, right +++; five, left ++++, right ++; one, left ++++, right +; and one, left ++++, right 0. These ten were in the calcified nodular group (subgroup "c"), in which death

TABLE X

DEGREE OF CORONARY SCLEROSIS

	ACUTE RHEUMATIC		RECURRENT RHEUMATIC		VALVE DEFORMITY SUBGROUP "A"		VALVE DEFORMITY SUBGROUP "B"		VALVE DEFORMITY SUBGROUP "C"		ADHERENT PERICARDIUM		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
L+++ R+++	0	0	0	0	0	0	0	0	3	1.5	0	0	3	0.5
L+++ R++	0	0	0	0	0	0	0	0	5	2.5	0	0	5	0.8
L+++ R+	0	0	0	0	0	0	0	0	1	0.5	0	0	1	0.2
L+++ R0	0	0	0	0	0	0	1	0.5	1	0.5	0	0	2	0.4
L++ R+++	0	0	0	0	0	0	7	4.0	16	8.1	0	0	23	3.8
L++ R++	0	0	0	0	1	1.2	3	1.7	8	4.1	1	5.0	13	2.2
L++ R+	0	0	0	0	0	0	0	0	1	0.5	0	0	1	0.2
L++ R0	0	0	0	0	0	0	0	0	3	1.5	0	0	3	0.5
L+ R+++	1	1.5	1	1.9	8	9.0	12	6.7	16	8.1	3	15.0	41	6.8
L+ R++	0	0	1	1.9	0	0	1	0.5	7	3.6	1	5.0	10	1.7
L+ R0	1	1.5	0	0	0	0	3	1.7	3	1.5	1	5.0	8	1.1
L+ R+	9	13.8	13	24.5	30	34.0	37	20.8	45	22.8	2	10.0	136	22.6
L+ R0	1	1.5	2	3.8	3	3.4	3	1.7	5	2.6	0	0	14	2.3
L0 R0	53	81.5	36	67.9	45	51.2	110	61.8	83	42.1	12	60.0	339	56.4
L0 R+++	0	0	0	0	1	1.2	1	0.5	0	0	0	0	2	0.4
Totals	65	99.8	53	100.0	88	100.0	178	99.9	197	99.9	20	100.0	601	99.9

occurred chiefly in the upper decades, the sixth and seventh. In most of the cases of rheumatic heart disease the sclerosis of the coronary arteries was less than +++ on the left or right. This was true in all of the cases of acute rheumatic endocarditis, recurrent rheumatic endocarditis, and adherent pericardium, and also in eighty-seven (98.9 per cent) of the eighty-eight cases in subgroup "a," in 170 (95.5 per cent) of the 178 cases in subgroup "b," and in 171 (86.8 per cent) of the 197 cases of subgroup "c" (valvular deformities).

There was no suggestion of any unusual degree of coronary sclerosis in the different groups of cases of rheumatic heart disease. The greatest amount was found in subgroup "c," in which death occurred in the later decades. There was, therefore, no evidence to support the idea that rheumatic infection of the heart may increase the incidence or degree of coronary sclerosis. In fact, there was really less coronary sclerosis than in cases in which death resulted from other causes. In the same series of autopsies (27,957) from which the 796 cases of rheumatic heart disease were taken, there were 1,066 cases in which death was caused by coronary sclerosis (3.8 per cent).

SUMMARY AND CONCLUSIONS

Rheumatic heart disease, including all forms immediately or indirectly caused by rheumatic infection, was a common, but not the most frequent, type of heart disease encountered in our study of 4,254 cases in which death resulted from noncongenital heart disease (796 cases, 18.7 per cent). Rheumatic heart disease was responsible for less than one-third of the cases of noninfectious heart disease (hypertensive heart disease, coronary sclerosis, and the various types of cor pulmonale), and its incidence was the same as that of bacterial endocarditis and cardiac failure secondary to syphilitic aortitis, combined.

There are four types of rheumatic heart disease, in two of which (acute rheumatic endocarditis and recurrent rheumatic endocarditis) the characteristic verrucous or rheumatic vegetations occur on the valves. In the second of these there are evidences of previous infection and scarring of the valves. These two types were not commonly encountered at autopsy (12.3 per cent and 9.5 per cent, respectively). The third variety, comprising cases of valvular deformities, caused the greatest number of deaths (73.5 per cent). In some of these cases the lesions were completely healed, and some showed signs of lingering infection. The calcified, nodular, aortic valve deformity, which is regarded by some as nonrheumatic, is, in our opinion, a rheumatic lesion. It comprised 40 per cent of all of the valve deformities. If it were not included among the rheumatic lesions, we would have to conclude that rheumatic infection of the aortic valve is uncommon. There were only a few cases in the fourth group, that in which it could be proved definitely that death had been caused by an adherent pericardium.

Death from acute and recurrent rheumatic endocarditis occurred chiefly in the early decades. Death from the incompletely or completely healed valvular deformities took place primarily in the middle decades, and, from the calcific, nodular, aortic valve deformity, in the later decades.

The sex incidence in this series was as follows: males, twenty-seven per thousand; females, thirty-one per thousand. The females died earlier than the males. This is probably because the valve which is most commonly involved in females is the mitral. Males and females with the same valve lesions die in the same decades. With a mitral deformity, compensation cannot be maintained as long in either sex as with an aortic valve lesion.

Little evidence for or against any of the theories concerning the nature of the infectious agent in rheumatic heart disease was discovered in this study. The type of inflammatory reaction within the valve was very similar to that which occurs in cases of frank, streptococcic, subacute bacterial endocarditis. This might be regarded as evidence in favor of the streptococcic theory of the etiology of rheumatic fever. The fact that the inflammatory reaction is a proliferative one does not definitely support the virus theory. It is even questionable whether the Aschoff nodule, which varies so decidedly in structure, and is by no means constantly present in cases of rheumatic heart disease, is sufficiently characteristic to justify the suspicion that it is caused by a specific infectious agent.

The valves of the left side of the heart are the ones which are chiefly involved (99.8 per cent). In 5.6 per cent of the cases there was right-sided involvement, but in all but one of these there was also a lesion of one or both of the valves of the left side of the heart.

The aortic and mitral valves were involved with equal frequency in the males. The incidence of involvement of the aortic alone, the mitral alone, and the aortic and mitral together, in the males, and of the aortic and mitral together, in the females, was about the same. Among the females, aortic involvement was less common than mitral involvement. The predilection for the mitral valve in females is not understood, but it helps to explain why the calcified, nodular, aortic deformity is common in old men.

Vegetations begin on the side of the valve where the spongiosa layer, which contains most of the blood vessels, is located, namely, on the ventricular surfaces of the aortic and pulmonic cusps, and on the auricular surfaces of the mitral and tricuspid valves. This suggests that the infection may be embolic in origin, but, in some cases, small vessels can be seen leading from surface indentations, which would indicate that infection may occur directly from the blood stream.

Valves which are thickened and scarred from repeated attacks of proliferative inflammation show a marked tendency to become calcified.

A calcified aortic valve has the same structure as a calcified mitral valve. Our study disclosed nothing to indicate that the calcified nodular aortic valve deformity differs etiologically and pathogenetically from the calcified mitral valve.

Auricular endocardial involvement was practically as common in cases of acute rheumatic endocarditis as in bacterial endocarditis.

Hypertrophy, which appears to be caused by increased work, was present in most of the cases; it was most marked when there was aortic involvement, and less pronounced when there were mitral lesions only. More hypertrophy was noted among the males, apparently because aortic lesions are more common among males than females.

Gross areas of fibrosis were rarely seen in cases of rheumatic heart disease, and, with a few exceptions, the coronary arteries were relatively free from severe sclerosis. There was no indication that rheumatic infection bears any causal relation to coronary sclerosis.

Pericarditis, either acute or in the form of adherent pericardium, was not a constant accompaniment of acute or recurrent rheumatic endocarditis. It was no more common than in subacute bacterial endocarditis. The presence of pericarditis cannot be used clinically in the differential diagnosis of acute rheumatic and subacute bacterial endocarditis. Death rarely resulted from the effects of an adherent pericardium alone.

Proliferative inflammation, of a nodular (Aschoff nodules) or diffuse type, was usually present. It may result in periarterial scarring. Such inflammation, although common, was not always present in cases of acute or healed rheumatic heart disease, but it was more common during the acute stage. The stigmata of rheumatic inflammation were practically as common in the valve and myocardium in the cases of calcified, nodular, aortic valve deformities as in the cases of mitral valve deformities.

Several important facts which might be of value clinically in the study of rheumatic heart disease emerge from the analysis of these 796 cases. Rheumatic heart disease causes slightly less than 20 per cent of all deaths from noncongenital cardiac disease, which is nearly twice the number caused by bacterial endocarditis, and nearly three times as many as result from heart disease secondary to syphilitic aortitis. As a rule, patients with acute rheumatic endocarditis die, not during an acute attack, but later, from the effects of valvular stenosis and insufficiency. Rheumatic heart disease affects males and females in about equal numbers. The males tend to live longer than the females. The aortic and mitral valves are involved with equal frequency in males, but mitral valve involvement greatly predominates in females. This means that the incidence of aortic valve lesions is higher in males than in females, and that that of mitral lesions is higher in females than in males. Both males and females survive

longer with an aortic lesion than with a mitral. All nonsyphilitic aortic valvular deformities which lead to cardiac failure appear to be rheumatic in origin. Tricuspid and pulmonic lesions, especially healed deformities, rarely occur without an associated aortic or mitral lesion.

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THE DIAGNOSIS OF CORONARY OCCLUSION AND MYOCARDIAL INFARCTION BY FLUOROSCOPIC EXAMINATION

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ALTHOUGH it is accepted that roentgenologic examination is a valuable and often indispensable adjunct in the diagnosis of certain types of heart disease, it has received comparatively scant attention in connection with disease of the coronary arteries, particularly coronary occlusion. As recently as 1934, it was remarked[1] that "roentgen studies have not been of any assistance in localizing, or, in fact, recognizing cardiac infarcts." Although the clinical manifestations of coronary occlusion are, as a rule, characteristic, the diagnosis is occasionally uncertain, and it is frequently difficult to evaluate the extent of myocardial involvement after recovery from the acute attack. Ordinary roentgenologic examination is of little help, for myocardial infarction, even when it is extensive, does not alter the cardiac contour unless marked enlargement or a ventricular aneurysm has resulted. However, roentgenologic methods which enable one to watch ventricular contraction offer greater promise, and it is the object of this report to show that impaired contraction of the left ventricle can be detected by simple fluoroscopic examination in a majority of cases of occlusion of a coronary artery.

That coronary occlusion produced changes in myocardial contraction was recognized experimentally as early as 1698, by Chirac,[2] and by a number of investigators[3-7] in the nineteenth century. However, a detailed description of these changes was lacking previous to the recent investigation of Tennant and Wiggers.[8] Employing the myocardiograph, they found that, immediately after occluding branches of the coronary arteries, in dogs, the area of muscle which was rendered ischemic ceased to contract, and paradoxical (reverse) movements occurred, i.e., the ischemic area bulged passively while the remainder of the ventricle contracted normally.

In man, the movements of the heart can be studied by means of fluoroscopy or roentgenkymography. There have been few recorded fluoroscopic observations of the effect of coronary artery occlusion on the contractile movements of the heart, except when the infarct has been extensive enough to result in the formation of a ventricular aneurysm. Impaired pulsation and systolic expansion have frequently been recognized fluoroscopically in such cases.[9-13] Libman[13] and Levene and

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his coworkers[14] observed localized impairment of contraction of the left ventricle in cases of coronary artery disease, but did not describe the systolic expansion (reversal of pulsation) which we found in fifty per cent of our cases of coronary occlusion,[15, 16] and which we consider pathognomonic of infarction. The senior author[16] has used fluoroscopic means of detecting coronary occlusion routinely for at least five years. Roentgenkymographic studies, also, have indicated that systolic expansion of the infarcted area characteristically occurs.[17, 18]

MATERIAL STUDIED

A fluoroscopic and roentgenkymographic study of ninety-five patients was made; this series comprised eighty cases of coronary occlusion and fifteen cases of coronary sclerosis and angina pectoris. The roentgenkymograms were taken immediately after the fluoroscopic examination. For control purposes, a large number of normal subjects were examined fluoroscopically, and, in thirty-five of these, roentgenkymograms were obtained. The patients with coronary occlusion were studied at intervals ranging from one month to six years after the acute attack. In twenty-four subjects with normal hearts or with cardiac infarcts, cineroentgenographic studies were made.

TECHNIQUE

A Patterson B-type fluoroscopic screen was employed, with the usual illumination for fluoroscopy (70-80 K.V. and 4 to 5 Ma.). Proper accommodation was found to be essential for study of the cardiac movements. After inspection of the size, shape, and position of the heart and great vessels, the size of the fluoroscopic screen was reduced so that it included only the left border of the heart. The time relationship of the pulsations was established by comparing the movements of the left ventricle with those of the aorta and pulmonary artery. Normally, the arterial pulsations are opposite in phase to those of the ventricle; the aorta expands while the ventricle contracts, and there is an inthrust of the entire left ventricular border, together with elevation of the apex and diaphragmatic surface of the heart (Fig. 1*A*). The medial movement of the upper part of the left ventricular border may slightly precede the inthrust of the apical region. Following examination in the postero-anterior position, the subject was rotated by degrees into the left oblique position, and the movements of the lateral and posterior walls of the left ventricle were studied successively.

The contractile movements of the heart were observed at the end of a moderately deep inspiration. In addition to immobilizing the diaphragm, this procedure slows the heart rate, and thus facilitates the examination, for a rapid heart rate makes it difficult to visualize the ventricular movements in detail. The patient was instructed not to strain, for this, by increasing intrathoracic pressure, may decrease the venous return to the heart and thereby reduce ventricular ejection and pulsation.

Several maneuvers may be employed when the details of the cardiac movements are not very clear. It is occasionally helpful to magnify the movements by drawing the screen away from the patient, particularly when the pulsations are of small amplitude. The presence of apical pericardial fat may obscure contraction and give the impression of diminution or absence of pulsation; one must therefore look within the fat pad to observe the ventricular movements. Since the study of ventricular pulsation is concerned even more with uniformity of contraction along the left ventricular border than with the amplitude of contraction, orientation as to time of contraction is of utmost importance. This may be attained by auscultation; a Bowles diaphragm is held to the patient's chest in the fourth intercostal space. Normally, the inthrust of the ventricle is synchronous with the first heart sound.

A. *B.* *C.*

Fig. 1.—Outline of the heart and great vessels in systole and in diastole, as determined by fluoroscopy. The unbroken line represents diastole, the dotted line, systole. *A*, Normal contraction. The left ventricle contracts uniformly in systole, with expansion of the aorta and pulmonary artery. *B*, Impaired contraction. While the upper half of the left ventricular border contracts normally, practically no pulsation is visible over the lower left ventricular border within the infarcted area. *C*, Reversal of pulsation (systolic expansion). There is loss of uniformity of left ventricular contraction. While the upper part of the left ventricular border contracts normally, the infarcted area above the apex does not contract, but is passively expanded by the elevated intraventricular pressure during systole.

When the heart rate is rapid, temporary slowing may be induced by pressure on the carotid sinus; this increases the magnitude of ventricular contraction and facilitates the examination.

The roentgenkymograms were obtained with a multiple-slit lead grid of the type described by Stumpf.[19] The slits were 12 mm., and, in some cases, 18 mm., apart, thereby visualizing the pulsations of points at closely spaced intervals along the heart border. The duration of exposure was 1.5 seconds, so that one to three complete cardiac cycles were recorded, depending on the heart rate. Exposures were taken in the posteroanterior and left oblique (about 25°) positions.

Motion pictures (Fig. 2) were made with a standard camera which had a film speed of 16 exposures per second. Intense illumination of the fluoroscopic screen was necessary for good photographic contrast. The roentgen factors were 75 Ma. at 100 K.V. for an exposure of two to three seconds. The film was serially reprinted for motion picture projection, which permitted a longer strip to be studied.

RESULTS

Coronary Occlusion.—Localized abnormalities in pulsation were observed fluoroscopically in fifty-nine (73 per cent) of the eighty cases of myocardial infarction. These consisted of complete or partial reversal of contraction in forty cases (50 per cent), and absence or diminution of pulsation in nineteen (23 per cent) (Table I).

TABLE I

TYPES OF VENTRICULAR CONTRACTION IN EIGHTY CASES OF CARDIAC INFARCTION

	FLUOROSCOPICALLY	ROENTGENKYMOGRAPHICALLY
1. Normal	21	16
2. Reversal of Pulsation	40	42
a) complete	29	25
b) partial	11	17
lag	8	7
doubling	3	10
3. Impaired Pulsation	19	22
a) absent	2	7
b) diminished	17	15
Total	80	80

Reversal of pulsation was the most common and definite abnormality in ventricular contraction associated with myocardial infarction. It was recognized by a loss of uniformity of contraction along the left ventricular border; as the normal portion of the ventricle contracted synchronously with the expansion of the great vessels during systole, the weakened myocardium at the site of the infarct was seen to expand passively as a result of the sudden rise in intraventricular tension (Figs. 1*C* and 2). This abnormality frequently appeared as a wavelike movement along the border of the left ventricle (Fig. 1*C*). Similar observations were made in three cases of ventricular aneurysm. In twenty-nine cases the reversal of pulsation was complete; in eleven others it was incomplete, and appeared only as a localized lag of systolic inthrust, or as a double systolic pulsation. Localized diminution or complete absence of

pulsation was also frequently observed (Fig. 1*B*), but these changes were less definite and significant than the systolic expansion.

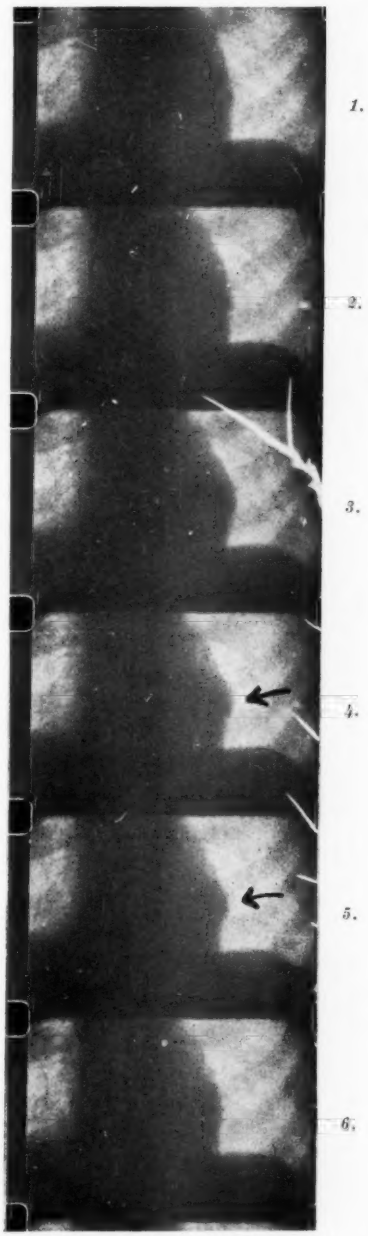


Fig. 2.—Continuous strip from cineroentgenograms in a case of cardiac infarction. Frames *1*, *2*, and *3* represent the heart in diastole. During systole, shown in frames *4* and *5*, there is a localized bulge of the left ventricular border above the apex which results from passive expansion of the infarcted area by the heightened intraventricular pressure. With the end of systole (frame *6*), as the intraventricular pressure abruptly falls, reducing the tension on the infarcted area, the left border again resumes an unbroken contour.

The abnormalities in contraction were most common over the lower left ventricular border, particularly in the apical and supra-apical regions (Fig. 3). In a few cases the changes were limited to the mid-region and upper section of the left ventricular border. The abnormalities were observed more frequently and with greater certainty in the posteroanterior than in the left oblique view; rarely, they were limited to the latter view. Thus, of the fifty-nine cases in which there was an abnormal pulsation, it was seen in the posteroanterior view alone in thirty-eight cases, in both posteroanterior and left oblique views in eighteen cases, and in the left oblique view alone in only three cases.

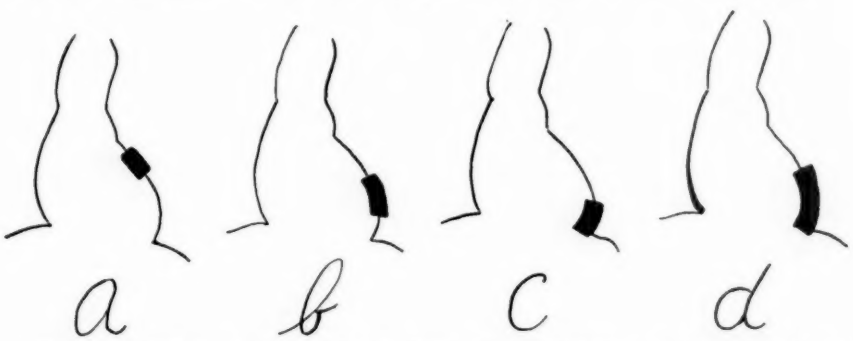
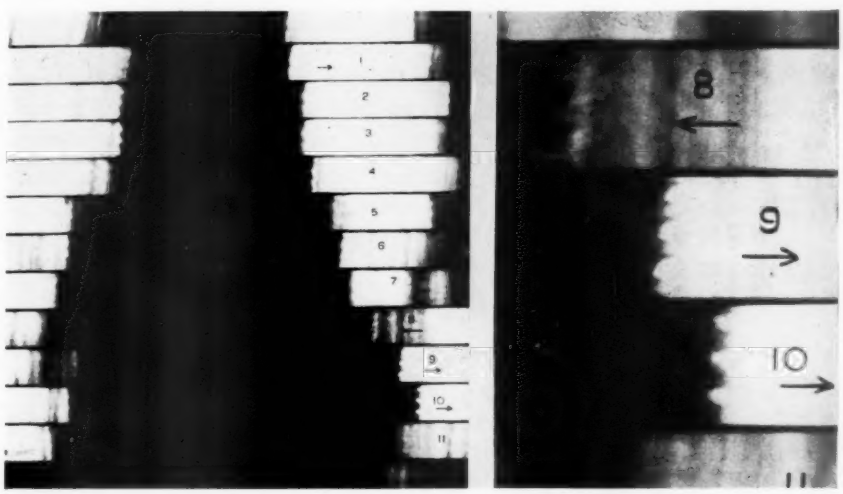


Fig. 3.—Location of abnormal pulsations fluoroscopically. *a*, Upper region of left ventricular border (4 cases); *b*, Supra-apical segment of left ventricle (17 cases); *c*, Apex of left ventricle (13 cases); *d*, Lower half of left ventricular border (25 cases).

Similar abnormalities in left ventricular pulsation were revealed by kymographic examination (Fig. 4). Comparison of the fluoroscopic and roentgenkymographic observations in the posteroanterior position showed complete agreement between the two methods in sixty-seven of the eighty cases. In five cases, definite abnormalities were present in the kymogram which were not detected fluoroscopically. In only one case was the kymogram normal when the fluoroscopic findings were considered abnormal; however, in this instance the pulsation was merely diminished, not reversed. In the remaining seven cases both the fluoroscopic and kymographic examinations revealed an abnormal pulsation, but there was some discrepancy in the interpretation of the type of abnormality. For example, in several cases what was interpreted fluoroscopically as absence of pulsation appeared in the kymogram as reversal; in another instance, what seemed to be a lag fluoroscopically turned out to be a reversal in the kymogram. In the left oblique position fluoroscopic examination was somewhat less satisfactory, and in nine cases abnormalities which were recorded in the kymogram were not detected with the fluoroscope. In general, it is evident that the results of the two methods agreed well in all of their essentials. When the fluoroscopic results were not confirmed by the kymograph, the error was usually one of omission rather than commission.

An attempt was made to correlate the fluoroscopic observations with the electrocardiographic localization of the infarct (Table II). Electrocardiographically, the cases were divided into four groups: anterior wall infarction, thirty-eight cases; posterior wall infarction, sixteen; anterior and posterior wall infarction, thirteen; and atypical pattern, thirteen. Of the thirty-eight cases of anterior wall infarction, in twenty-two there was an abnormal ventricular contraction which was observed in the posteroanterior position in every instance, and also in the left oblique view in four of the cases. When there was infarction of the posterior wall, or of both anterior and posterior walls, the abnormal pulsation was seen in the left oblique position, as well as in the posteroanterior, in almost half of the cases. Although these observations suggest that abnormal contraction is frequently observed in the left oblique view when the infarct is situated on the posterior wall of the left ventricle, it should be emphasized that only rarely is the abnormality confined to this view, e.g., in only three of our cases.



A. *B.*

Fig. 4.—*A*, Roentgenkymogram from a patient with an old infarct of the anterior surface of the left ventricle, exhibiting the various types of abnormalities in left ventricular contraction. *B*, Magnification of movements of left ventricular border.

Segment *8*.—Normal ventricular contractions. There is an inward (mesial) movement of the upper portion of the left ventricle synchronous with outward (lateral) movement of the aorta (segments *1* and *2*).

Segment *9*.—Partial reversal of pulsation. The left ventricular border contracts in early systole, but immediately thereafter shows a lateral movement (systolic expansion). This appears fluoroscopically as a double systolic pulsation.

Segment *10*.—Complete reversal of pulsation. The mid-ventricular border shows a systolic expansion (lateral movement) which is synchronous with the normal mesial movement of segment *8* and with the expansion of the aorta.

Segment *11*.—Complete absence of pulsation of left ventricular border in the apical region.

Coronary Sclerosis.—Fluoroscopic studies were made on fifteen patients who had either a history of angina pectoris or electrocardiograms which suggested coronary artery disease, but gave no history of acute coronary occlusion. In ten cases the ventricular contractions were en-

TABLE II

COMPARISON OF ELECTROCARDIOGRAPHIC AND FLUOROSCOPIC LOCALIZATION OF INFARCTION

	ELECTROCARDIOGRAPHIC LOCALIZATION							
	ANTERIOR WALL		POSTERIOR WALL		ANTERIOR AND POSTERIOR		ATYPICAL PATTERN	
	F*	K*	F	K	F	K	F	K
Location of Abnormal Pulsation								
Normal	16	11	3	2	1	2	1	1
Posteroanterior View	22	27	11	11	12	11	11	11
a) upper left vent. border	0	1	1	1	1	1	0	0
b) supra-apical segment	8	7	3	4	2	1	4	4
c) apex	4	6	3	1	4	2	2	3
d) lower half left vent.	10	13	4	5	5	7	5	4
Left Oblique View	4	4	4	7	8	9	5	5
a) upper left vent.	0	0	2	4	2	2	0	1
b) lower left vent.	4	4	2	3	6	7	5	4

*F is fluoroscopy; K is kymography.

tirely normal fluoroscopically and in the kymograms. In two cases equivocal changes were observed by both methods. Of the remaining three cases, absence and partial reversal of pulsation were seen fluoroscopically in two, and were present in the kymogram in all. Although these patients had practically normal electrocardiograms, in each case a severe anginal syndrome was present, and it is probable that extensive myocardial disease accounted for the partial reversal.

Normal Subjects.—No abnormal pulsations were observed in the large control group of normal subjects who were examined fluoroscopically, and roentgenograms in thirty-five of these subjects were normal.

COMMENT

It is evident from these results that fluoroscopic examination affords a relatively simple and accurate method of detecting the presence of a myocardial infarct. Abnormalities in ventricular contraction may be observed in nearly three-fourths of the cases of coronary artery occlusion; they appear as a localized reversal (systolic expansion) in half of the cases, and as absence or diminution of pulsation in about one-fourth. The former has greater significance than the latter and may be considered pathognomonic of myocardial infarction. The reversal of pulsation is probably caused by a bulging of the weakened, infarcted area; this area is thrust outward by the systolic rise of intraventricular pressure, while the remainder of the ventricle contracts forcibly. The reversal may not be complete; it then appears as a localized lag of systolic contraction, or as a double systolic pulsation. Since, in normal persons, the inthrust of the upper left ventricular border slightly precedes that of the apex,[20] a slight lag of the supra-apical region must be interpreted with caution. Localized diminution or absence of pulsation must be regarded as abnormal, but not pathognomonic of infarc-

tion, and should not be confused with a normal apical pulsation which is obscured by a pericardial fat pad.

Although we think that reversal of pulsation is pathognomonic of myocardial infarction, we have observed it in a small number of cases of aortic valvular disease and long-standing hypertensive heart disease in which there was considerable cardiac enlargement. These abnormalities occurred chiefly when cardiac insufficiency and precordial pain were present, so that, although they were probably not indicative of actual infarction, it is likely that they were caused by myocardial disease. It is possible that there was an aneurysmal thinning of the myocardium in the apical region in these cases. Esser[21] noted impairment of apical contraction in cases of cardiac enlargement of all types.

Among the cases of myocardial infarction, the apical and supra-apical regions of the left border, that is, the anterior wall of the left ventricle, most frequently exhibited abnormal pulsation when either the anterior or the posterior wall was involved. Fluoroscopic examination, therefore, is not decisive in localizing the area of infarction, and it appears that the area of abnormal contraction does not always correspond to the area of infarction. The probable explanation for this is that damage at any point to the deep and superficial spiral muscles, which wind around the apical region of the left ventricle, may alter the leverage in contraction in such a way as to produce an abnormal type of pulsation at the apex. However, abnormal contractions in the left oblique position, as well as in the posteroanterior view, are more likely to occur with infarction of the posterior wall than with anterior wall infarction.

Our studies indicate that the results obtained fluoroscopically closely parallel those of roentgenkymography. In the few cases in which these methods disagreed, an abnormal pulsation was present in the kymogram but was not detected fluoroscopically. Although roentgenkymography has the advantage of being an objective method, it requires special apparatus and some experience in interpretation. Fluoroscopic examination, on the other hand, is a simple method which is available to all who are engaged in clinical medicine. Furthermore, it enables one to study the movement of the entire left ventricular border by gradually rotating the patient and making observations at different angles, whereas in the kymogram the movements of only one projection, or at most a few, are recorded. Thus, in one case, reversal of pulsation was detected fluoroscopically over the lower left ventricular border with the patient rotated in the left oblique position to an angle of 15° to 20°, but was not observed in other views, and roentgenkymograms which had been taken in the posteroanterior and full left oblique positions failed to reveal this abnormality. When a kymogram was taken at the proper angle, the reversal of pulsation was clearly recorded. Similarly, an aneurysm of the apex of the left ventricle was brought out fluoroscopically by rotating the subject slightly into the right oblique position.

The ideal procedure would be to make a fluoroscopic examination first, and then take roentgenkymograms at those projections in which abnormal pulsations of the left ventricular border are suspected.

Although contraction becomes impaired immediately following myocardial infarction, fluoroscopic examination is not likely to find wide application in the acute stage of coronary occlusion, for the patients are usually too ill for such examination. Occasionally, however, it may be helpful when the diagnosis is difficult, as in cases of progressively increasing angina pectoris, or when there are mild, atypical attacks. A problem of greater importance is to evaluate the extent of myocardial involvement immediately following recovery from an acute attack of coronary occlusion, and to detect the presence of infarction in patients who give a past history of such an attack, or of angina pectoris. Although the electrocardiogram is helpful in these cases, it is often inadequate, and further diagnostic aids, such as fluoroscopy, are welcome.

SUMMARY AND CONCLUSIONS

Fluoroscopic examination in a group of eighty patients with cardiac infarcts secondary to coronary artery occlusion revealed abnormalities in the contraction of the left ventricle in fifty-nine cases, or 73 per cent. This was evident as a localized impairment of pulsation along the left ventricular border which was best observed in the ordinary posterior anterior view, and most often in the apical, and particularly the supra-apical, region.

The abnormalities consisted of (a) complete reversal of pulsation (systolic expansion) (twenty-nine cases); (b) partial reversal, which appeared as a lag, or doubling, of systolic contraction (eleven cases); (c) absence of pulsation (2 cases); and (d) marked localized diminution of pulsation (seventeen cases).

An abnormal pulsation was seen in two out of fifteen cases of coronary sclerosis and angina pectoris in which there was no history of coronary occlusion. These abnormalities were not observed in any of a large group of subjects without heart disease who were examined as controls.

The fluoroscopic abnormalities corresponded closely with those observed in the roentgenkymograms which were taken immediately after the fluoroscopic examination in all cases. Cineroentgenograms, which were taken in twenty-four cases, also demonstrated the different types of abnormal pulsations.

A localized reversal of pulsation (systolic expansion) is considered pathognomonic of infarction when the heart is not considerably enlarged. When the heart is enlarged, the pulsations may be impaired near the apex in the absence of cardiac infarction, but even in such cases complete systolic expansion is only rarely observed.

It is concluded that fluoroscopic examination is a valuable and reliable method for detecting cardiac infarction following coronary artery

occlusion. The method is not advocated for use during the first days of the illness, but rather to help evaluate the degree of myocardial involvement after recovery from the acute attack. Since the changes in contraction may be permanent, fluoroscopic examination may be the means of obtaining evidence of previous infarction in patients with angina pectoris, or in any patient whose history suggests that he has had an attack of coronary artery occlusion.

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THE EFFECTS OF WHOLE BILE AND BILE SALTS ON THE INNERVATED AND THE DENERVATED HEART

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THE effect of whole bile and bile salts on the perfused heart was reported recently by the authors.[1] The results obtained indicated that there is a direct action of these agents on the myocardium. However, since the slowing of the heart of the intact animal and other changes in rhythm which are produced by bile constituents have been attributed, by some authors, to vagal reflexes, it seemed desirable to compare the effect of the administration of whole bile and of bile salts on the innervated and the denervated heart in otherwise intact animals. In this paper we are reporting the results of a study of the blood pressure, heart rate, and electrocardiographic changes after the intravenous administration of whole bile and bile salts to dogs with innervated hearts and to others with denervated hearts. In order to eliminate the influence of anesthetic agents, a few experiments also were performed on trained dogs.

Still[2] found that neither the administration of atropine nor double vagotomy materially changed the effect on the vascular system of administering bile constituents intravenously to dogs. Baltaceano and Vasiliu[3] indicated that the hypotensive effect of sodium taurocholate was produced through the reflexogenic zones of the carotid sinus and the cardio-aortic region. Nevertheless, they stated that bradycardia could be produced by direct action of sodium taurocholate on the myocardium, as well as reflexly through the carotid sinus. Buchbinder[4] produced obstructive jaundice in pups by ligating the common bile duct, and attributed the resulting bradycardia to a reflex through the vagus. He stated that inversion of the T wave was the most frequent abnormality which appeared in the electrocardiogram. He did not detect any prolongation of either the P-R interval or the QRS complex. Horrall[5] stated that Röhrig cut the vagi, and that Landois was the first to give bile intravenously following section of the vagi and sympathetic nerves. Röhrig[6] found that the intravenous injection of bile caused slowing of the heart before, as well as after, cutting the vagi. However, the slowing was slight after the vagi were cut. He concluded that the bile damaged the excitomotor ganglion of the heart. Landois[7] produced slowing of the heart by the intravenous administration of bile after having sectioned the vagi and sympathetic nerves, and concluded that the bile acted directly on the heart.

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METHODS

Two series of acute experiments were performed on apparently normal dogs, which weighed from 10 to 18 kg. The animals were anesthetized by the intravenous administration of 25 mg. of pentobarbital sodium (nembutal) per kilogram of body weight. All of the procedures were the same in the two series of acute experiments, except that in one group of animals bilateral denervation of the heart was done, according to the method of Cannon, Lewis, and Britton,[8] immediately after anesthesia had been induced. After the operation was completed, the animals breathed without aid.

The femoral artery was cannulated, and the blood pressure was recorded by a standard mercury manometer and kymograph. A sufficient quantity of bile for all of the experiments was collected, with aseptic technique, from the gallbladders of dogs, and filtered through sterile gauze into a sterile flask. Five per cent solutions of each of the bile salts, sodium taurocholate and sodium glycocholate, were made in Ringer's solution. The bile and the solutions of bile salts were given intravenously in appropriate doses. The blood pressure was recorded continuously, and electrocardiograms were taken before, during, and after each injection throughout each experiment.

At the end of each experiment, pieces of cardiac tissue were removed and fixed in formalin for histologic study.

In order to obtain a series of observations which could not have been influenced by anesthesia, operative trauma, or an accumulative effect of repeated doses of bile, similar experiments were performed on a group of trained dogs over a period of several weeks. To make it possible to measure the blood pressure in the carotid artery repeatedly, over long periods, animals were prepared in the following manner: Aseptically, under ether anesthesia, both carotid arteries were separated carefully from the carotid sheaths for a distance of about 5 cm. The muscles surrounding each carotid sheath were sewed together dorsad to the vessels in such a way that the arteries lay superficially under the skin, making their pulsations easily palpable. The dogs made an uneventful recovery, and, after training, would lie quietly on the table. Records of both systolic and diastolic blood pressures were obtained by the method of Hamilton, Brewer, and Brotman,[9] and electrocardiograms were taken simultaneously before, during, and after the injection of bile into the lateral saphenous vein.

In order to observe the effects of the injection of bile on the denervated heart of the trained animal, the heart of one animal was denervated several weeks before the subcutaneous transposition of the carotid arteries. After the dog had recovered completely from both operations, it was trained to lie quietly on the table during the simultaneous recording of the blood pressure and electrocardiogram before, during, and after each injection of bile.

RESULTS

A prompt decrease in blood pressure followed every effective dose of bile or bile salts in the acute experiments. With repeated doses, the blood pressure was gradually reduced below the effective physiologic level. The gradual decrease in blood pressure which resulted from the successive doses of bile or bile salts was practically the same in dogs with denervated hearts as in those with innervated hearts (Table I). The only noticeable difference was that in dogs with innervated hearts the blood pressure after injection usually tended to return to its previous level, whereas in the ones with denervated hearts it did not.

The results of the experiments on the trained dog were similar. When repeated doses of whole bile, ranging from 0.25 c.c. to 1.0 c.c. per kilo-

gram of body weight, were given intravenously, over a period of several days, no marked decrease in blood pressure resulted until a dose of 1 c.c. per kilogram of body weight was given (Fig. 1). The rate of both the denervated and the innervated heart slowed markedly under the influence of the large doses of bile, in spite of the fact that a slight, transient tachycardia followed the initial, small doses. Different types of cardiac irregularities were recorded in the electrocardiograms. In several experiments cardiac standstill was observed for several seconds, soon after the administration of a large dose of the bile constituent (Fig. 2).

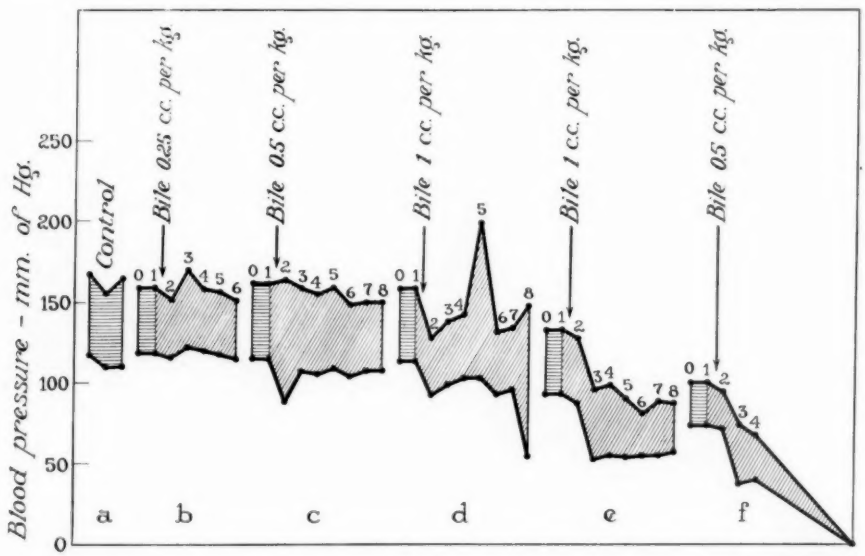

Fig. 1.—Systolic and diastolic blood pressures, measured by puncturing the carotid artery of a trained dog with an innervated heart, showing the effect of the intravenous administration of whole bile from a dog's gallbladder. Observations were made at intervals over a period of several days. The upper border of the curve represents the systolic, the lower, the diastolic, and the shaded area, the pulse pressure, on the same dog. *a* represents the control pressure, taken on three different days before any bile was administered. *b*, *c*, and *d* represent the observations made on one day. *e* and *f* were taken on the same day, because, after the injection of bile in *e*, the animal went into coma, and did not wake up even in two hours after the injection. Then blood pressure records were taken again, and a smaller dose of bile was given; a few additional records were made before the animal died. *0* to *1* represents the level of the pressure record on the same day, immediately before the injection of bile. The arrow indicates the intravenous injection of the bile, and the subsequent numbers, *2*, *3*, *4*, and so forth, indicate blood pressure records which were taken, respectively, at half-minute intervals after the injection.

At necropsy the heart appeared flabby and dilated. Histologic examination revealed rupture of small vessels and interstitial hemorrhages into the myocardium. In a few sections there was only evidence of congestion of vessels, with moderate to severe dilatation. Centrifugalization of specimens of blood revealed various degrees of hemolysis.

SUMMARY

The effects of the intravenous administration of whole bile and bile salts on the blood pressure and the electrocardiogram were studied

in a series of acute experiments, under pentobarbital sodium (nembutal) anesthesia, on normal dogs and on dogs with denervated hearts; the same methods and technical procedures were employed in both cases. Similar observations were made over a period of several weeks on normal, trained dogs, and on one trained dog with a denervated heart; this permitted us to make repeated observations which could not have been influenced by anesthesia, operative trauma, or an accumulative effect of successive injections of bile.

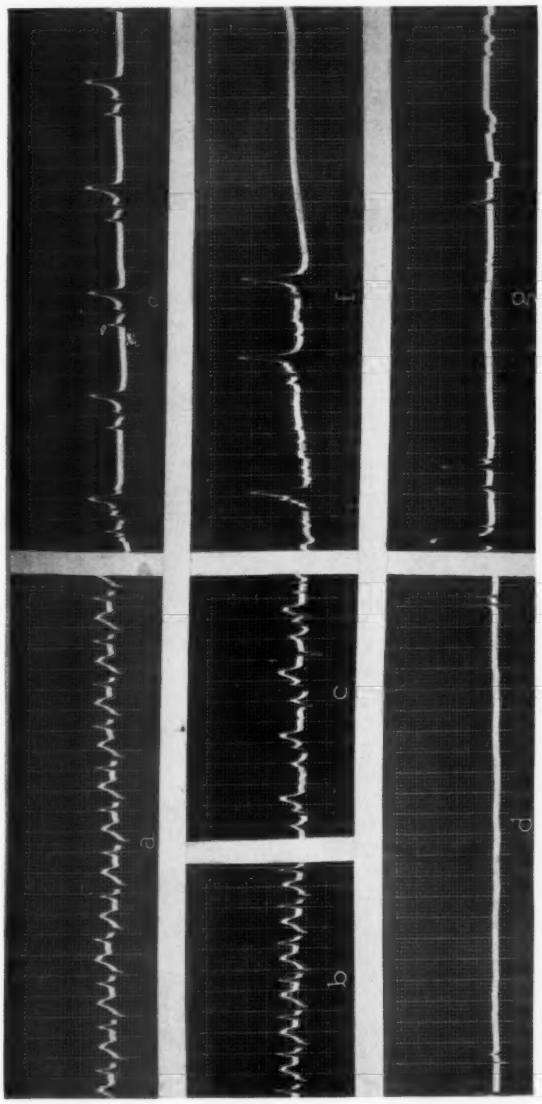

Fig. 2.—Electrocardiograms (Lead II) from a dog with innervated heart under the influence of bile, from a dog's gallbladder, which was administered intravenously. Tracings were made: *a*, before any bile was given; *b*, immediately after administration of 0.25 c.c. of bile per kilogram of body weight; *c*, immediately after administration of 0.8 c.c. of bile per kilogram of body weight; *d*, immediately after administration of 1 c.c. of bile per kilogram of body weight. The heart stopped for twenty-eight seconds, after which it resumed activity at a slow rate, as seen in *e*; *e*, five minutes after *d*; *f*, eight minutes after *d*; note the marked slowing; *g*, fourteen minutes after *d*; note the irregularities.

There were no detectable electrocardiographic differences between the effects of whole bile and bile salts on the innervated and the de-

TABLE I

REPRESENTATIVE DATA OBTAINED FROM ACUTE EXPERIMENTS ON THE INNERVATED AND DENERVATED HEART

DOSE PER KG. OF BODY WEIGHT	HEART RATE PER MINUTE		BLOOD PRESSURE, MM. OF MERCURY			
			INNERVATED HEART		DENERVATED HEART	
	INNERVATED HEART	DENERVATED HEART	BEFORE EACH INJECTION	AFTER EACH INJECTION	BEFORE EACH INJECTION	AFTER EACH INJECTION
Control	200	150	124	---	128	---
Sodium glycocholate, mg.						
29	170	150	124	114	128	102
37	160	150	128	102	138	106
45	160	150	126	103	134	100
56	180	150	120	92	126	88
63	170	140	115	78	110	86
67	160	140	108	74	102	80
74	140	140	104	61	90	70
74	130	130	96	50	76	62
74	110	120	74	38	82	58
74	110	110	60	33	58	50
74	110	100	60	34	60	44
82	70	90	46	25	62	52
85	20	80	47	0	60	50
92	35	40	36	0	54	44
Control	130	130	148	---	134	---
Sodium taurocholate, mg.						
29	140	150	148	134	134	132
35	140	150	148	144	147	121
43	140	150	152	146	143	116
53	170	140	158	136	144	108
61	150	130	152	138	140	108
64	150	150	158	140	146	112
71	160	160	163	106	154	116
71	160	160	154	135	160	132
71	160	140	160	128	154	120
71	170	150	162	123	138	104
71	180	150	150	120	160	104
71	170	150	152	106	151	96
79	160	150	133	97	128	80
82	150	140	136	76	102	66
89	130	140	122	60	91	53
89	90	120	118	49	73	49
89	40	120	106	33	54	43
89	10	100	50	22	36	30
89	?	60	47	22	20	13
Control	150	140	130	---	124	---
Bile, c.c.						
0.25	180	150	130	84	124	82
0.50	160	150	136	93	156	84
0.70	180	150	130	88	125	78
0.80	150	150	110	56	98	56
1.00	100	140	96	50	75	53
1.00	30	80	84	0	51	42

nervated heart; the irregularities and slowing of the rate of the heart were similar. During the period of gradual recovery from the hypotensive effect brought about by the first injections of bile constituents, the blood pressure of the dogs with denervated hearts usually did not return to its previous level, but the blood pressure of the dogs with innervated hearts, usually tended to do so. In both the normal animals and those with denervated hearts, approximately the same, gradual, hypotensive effect was produced by the intravenous administration of repeated doses of whole bile or bile salts. The injections finally led to failure of the heart, fall of blood pressure, and death of the animal.

Our observations on the innervated heart differed so slightly from those on the denervated hearts of otherwise intact dogs to which whole bile or bile salts were administered intravenously, that it appears justifiable to conclude that whole bile and bile salts can produce practically the same hypotensive effect and cardiac changes, such as bradycardia and disturbances in rhythm, in the absence, as well as in the presence, of the cardiac autonomic nerves.

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Department of Clinical Reports

MITRAL STENOSIS AS A CAUSE OF ANGINA PECTORIS

Report of Two Cases, With Necropsy

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RHEUMATIC aortic insufficiency has long been recognized as a cause of angina pectoris. There are, however, singularly few case reports of mitral stenosis in association with angina, and in some of these the anginal syndrome was attributed to independent disease. Although the diagnosis of mitral stenosis offers little difficulty, Gallavardin[1] has said that before one can hold that lesion responsible for the pain, it is necessary to demonstrate post mortem that there was no other.

Kourétas,[2] in 1924, culled from the literature only three cases of angina pectoris in which uncomplicated mitral stenosis was diagnosed at autopsy. To these must be added those of Levine[3] (one case), Sternberg[4] (one case), Telia[5] (one case, with microscopic studies of coronary arteries), and Hochrein[6] (one case). Cases in which no autopsy was done have been reported since 1923 by the following: Kourétas[2] (eleven cases from Gallavardin's service); Montes-Pareja[7] (one case); Castex and Beretervide[8] (four cases); Liesch[9] (two cases); Hochrein[6] (two cases); Doumer[10] (one case); Alvarez and Velasco[11] (one case); Lian, et al.[12] (two cases), and Chapuy and Brun[13] (one case).

Of the various theories which have been advanced to explain angina pectoris in cases of mitral stenosis, that of a failing heart muscle is the simplest, and therefore seems to me to be the most probable. That is to say, the right ventricle and left atrium, which are taxed to force blood through the stenosed mitral orifice, are unable to meet unusual demands; the left ventricle is therefore unable to sustain a high enough head of pressure in the root of the aorta to supply the coronary arteries with a sufficient amount of oxygenated blood.

REPORT OF CASES

Case 1.—B. T. was born in 1916, and was the second of eleven children. During the first two months of this pregnancy her mother was ill with pneumonia.

When she was six months old she had a cold, and cyanosis and dyspnea were then observed for the first time. Thereafter, marked cyanosis was occasionally observed after exertion, or in association with infections of the respiratory tract. Palpitation, shortness of breath, and precordial aching were brought on regularly by exertion, and not infrequently she experienced severe, stabbing, retrosternal pain. She felt tired constantly. After walking half a mile to school, she always had to

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rest for several minutes before she could go upstairs; at times it was necessary for her to stop and lie down. She coughed up blood occasionally, usually when she was having an unusual amount of dyspnea; she had not, however, experienced epistaxis. She suffered a great deal with migraine.

Examination.—B. T. was first examined by me in 1931. She was a poorly developed, poorly nourished girl, and was slightly cyanotic. Moderate kyphosis and precordial bulging were noticeable. A diastolic thrill was palpable just within the apex, and a diastolic shock was felt in the pulmonary area. The area of cardiac dullness was increased. At the apex, a low-pitched, rumbling murmur, beginning in mid-diastole, was followed by a long, harsh, systolic murmur which was transmitted medially. The pulmonic second sound was extremely accentuated, but there was no murmur in the pulmonic region. The systolic murmur could be heard faintly in the left interscapular space. During the period of hospitalization the pulse rate ranged from 74 to 150; it was usually between 110 and 120. The systolic blood pressure varied from 98 to 104, and the diastolic from 72 to 76.

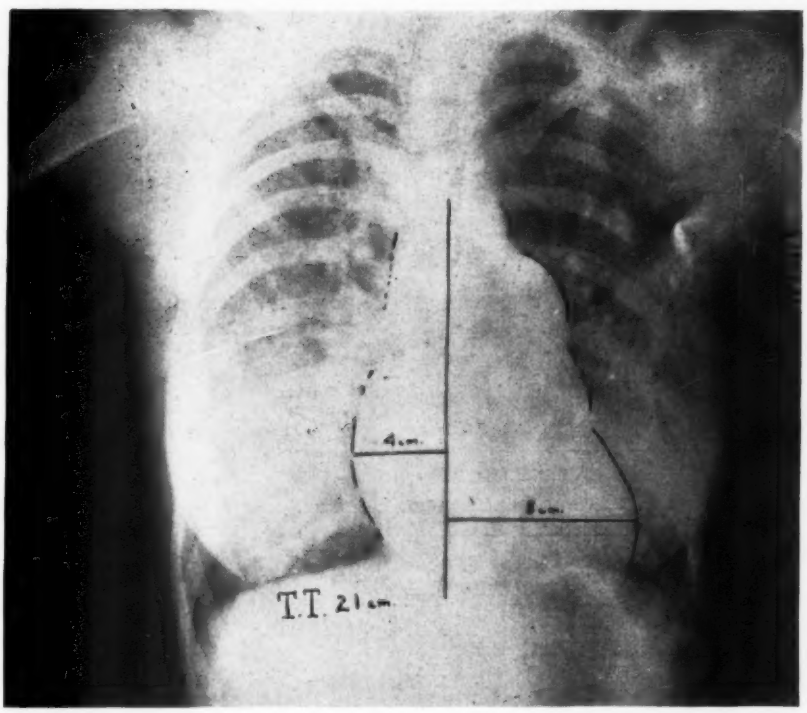

Fig. 1.—Teleoroentgenogram of B. T., in March, 1931. Note the prominence of the pulmonary conus and artery, the increase in the density of the hilar vessels, and the enlargement to the right. The aorta and the tip of the left atrium can also be made out.

The teleoroentgenogram is shown in Fig. 1. Fluoroscopically, the pulmonary trunk could be seen to expand during systole, and alterations in the density of the hilar vessels, particularly on the right, were observed with the heart beat. The electrocardiogram exhibited only right axis deviation.

Diagnosis.—Although signs of mitral stenosis were evident, congenital mitral stenosis is rare, and the roentgenologic appearance was not typical. B. T.'s symptoms dated back to infancy, and the diagnosis of congenital heart disease therefore seemed warranted.

Course.—She spent most of her waking hours reading, day-dreaming, and writing verse. However, she continued to have frequent and ever more excruciating attacks of anginal pain; she realized that she might die in any one of them, and wished as much as an intensely devout girl could that she might be released from her suffering.

She spent May 8, 9, and 10, 1936, at a religious revival which caused her great emotional excitement; this was climaxed when her uncle, who was a drunkard, promised to reform. After walking two blocks from the streetcar on her return home the following day, she collapsed and began to cough up frothy, bloody sputum. The heart rate ranged from 140 to 150 until her death ten hours later.

Necropsy.—The general outline of the heart was that of an inverted keystone, as shown in the roentgenogram. The external diameter of the pulmonary artery was 3 cm. There was no communication between the atria or between the ventricles. The ductus arteriosus was closed. The average thickness of the wall of each ventricle was 12 mm. The tricuspid valve was normal, measuring 8 cm. The inner circumference of the pulmonic valve was 8 cm. The pulmonary artery appeared normal, except for its dilatation, and so did the proximal parts of its main branches. The mitral valve was deep, tremendously thickened, and stenosed; its orifice measured about 6 by 8 mm. The inner circumference of the aortic valve was 5.5 cm. The aorta looked normal, and there was no anomaly in the origin of the coronary arteries or of the great vessels. Grossly the heart muscle seemed healthy. The lungs were almost solid with edema.

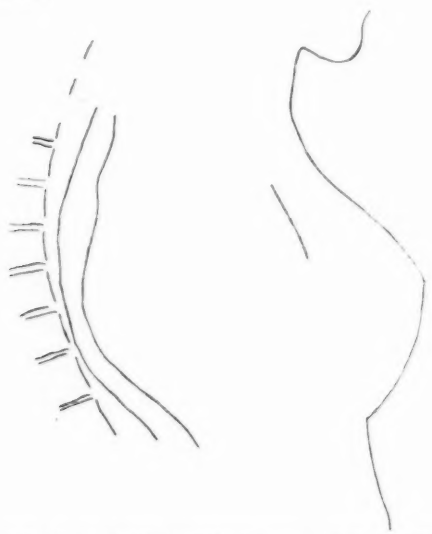

Fig. 2.—Tracing of the lateral teleoroentgenogram of B. T. The displacement of the esophagus, which was visualized with barium, reveals the degree of dilatation of the left atrium.

Case 2.—R. D., a newspaperman, aged 36, was first examined by me on March 15, 1933. In 1915, after two weeks of rheumatic fever, he resumed a very active life. During the course of an examination for life insurance, in 1920, a heart murmur was discovered. In 1928 he began to notice that playing eighteen holes of golf exhausted him. At about the same time he experienced an excruciating pain which began in the left humerus and radiated back to the precordium and down to the xiphoid, and was associated with dyspnea, palpitation, and, at times, tachycardia. These attacks, which lasted perhaps four minutes, would terrify him. He had four or five similar attacks from 1928 to 1930. Christmas night, 1932, he experienced his first attack of nocturnal orthopnea. By that time his endurance had decreased to such an extent that he had had to give up golf, and walking two blocks uphill would tire him.

Examination.—In March, 1933, the heart was slightly enlarged to the left, but no thrill was made out. At the apex, a soft diastolic murmur, which merged into a presystolic murmur, and a rough systolic murmur were noted. The pulmonic second sound was markedly accentuated. The blood pressure was 104/74; the pulse rate was 92. The teleoroentgenogram revealed the typical mitral configuration, without great enlargement.

Diagnosis.—Aside from the history, the physical signs justified the diagnosis of rheumatic heart disease, with mitral stenosis. The anginal attacks were attributed to rheumatic changes, such as those described by Karsner and Bayless,[14] in the coronary arteries. In view of the steady lessening of the cardiac reserve during the preceding five years, a rather grave prognosis was given.

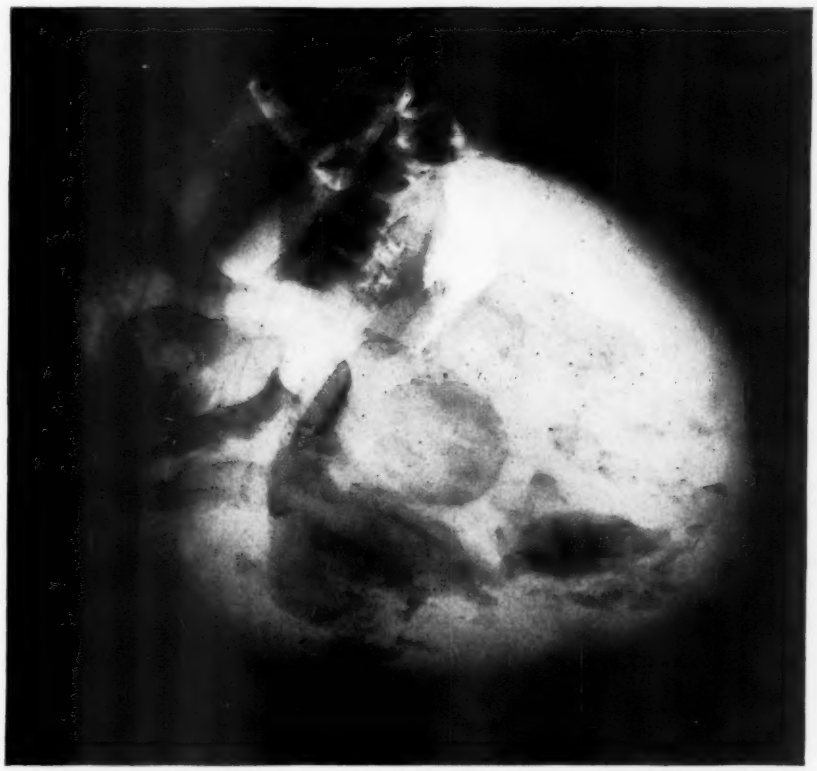

Fig. 3.—Post-mortem anteroposterior roentgenogram of the heart of R. D., showing the calcification of the mitral valve.

Course.—He continued to have severe attacks of pain, usually following exertion. In none which I observed did the heart rate exceed 120. Severe congestive failure had developed by September, 1936. After this, in spite of staying in bed most of the time, with rigid restriction of fluid and salt intake, and frequent injections of salyrgan, his condition grew steadily worse.

In the summer of 1938 there were several paroxysms of tachycardia, with a heart rate of about 180. These attacks were not associated with pain, although he expected to die in each one. Each of these subsided after an injection of 5 grains of soluble phenobarbital. He had several alarming pulmonary emboli, but only two attacks of angina, in 1938. The abdomen was tapped, and 8,000 to 10,000 c.c. of fluid removed, in June, July, and August, and Southey tubes were used from Aug. 11 until his death, a week later.

The systolic blood pressure was usually from 90 to 100, with a pulse pressure of 20, or less; the best reading was 124/88, and the poorest, a few weeks before death, 84/76.

The electrocardiograms were of interest only in that they showed a gradual decrease in the amplitude of the QRS complexes. Successive teleoroentgenograms showed a gradual increase in the size of the heart. Before his death, marked curvature of the nails had developed.

Necropsy.—The body was waterlogged. Several pulmonary infarcts, in various stages of resolution, were observed. The heart weighed 547 Gm. The mitral valve was thickened, calcified, and stenosed; the opening measured approximately 6 by 8 mm. The coronary arteries were normal. The left ventricle was scarred and relatively atrophic. The pulmonary arteries appeared to be normal.

Microscopic Examination.—Microscopic examination by Dr. Francis P. Parker revealed extensive scarring of the myocardium, but no coronary lesions. The pulmonary arteries were normal.

Comment.—It is worthy of note that auricular fibrillation was never detected in this patient; even during the paroxysms of tachycardia, in the last three months of his life, the heart beat was regular.

DISCUSSION

Both of these patients with mitral stenosis suffered, for a number of years, frequent, severe attacks of classical angina pectoris, including the sense of impending dissolution.

In spite of the difference in sex, age, social position, and educational advantages, these two patients had many things in common. Each had a family history of psychic instability, and each was a thin, highstrung, highly emotional, at times hysterical, person.

The first patient never enjoyed much cardiac reserve, but she never exhibited frank signs of congestive failure until the terminal pulmonary edema. The second patient had his first signs of grave myocardial insufficiency eight years after the onset of minor symptoms, and twenty-one years after the attack of rheumatic fever.

Each was subject to attacks of paroxysmal tachycardia. During the course of an examination the girl's heart rate would suddenly increase to 140 or 150, but she would have no pain. The man might suffer extreme pain in the left arm when his heart rate was not more than 120, but during three of his paroxysms, when the heart rate was 180, he was observed to have pronounced precordial oppression, dyspnea, and fear of impending death, although true anginal pain was conspicuously absent. It is quite possible, however, that the anginal crises were often precipitated by tachycardia.

In the first case, perhaps the most serious obstruction was in the pulmonary circulation and was caused by a primary sclerosis of the lesser system such as Posselt[15] has described. It is possible that the primary lesion was congenital mitral stenosis, and that this obstruction raised the pressure in the pulmonary arteries to such an extent that eventually they underwent secondary sclerotic changes. In the second case there was no serious disease of the pulmonary artery or its branches. The mitral valve was calcified, and there was extensive fibrosis of the myo-

cardium. In both cases the coronary arteries were grossly normal, and in one of them they were normal microscopically, also.

It would appear, then, that the anginal seizures in both cases were caused by the fact that the left ventricle did not receive blood fast enough to enable it to sustain in the proximal aorta a pressure adequate to fill the coronary arteries when these arteries were called on to meet extra demands.

It is suggested that, if more attention were paid to symptomatology in cases of rheumatic heart disease, angina pectoris would be reported more often.

SUMMARY

Two cases of angina pectoris which was associated with, and probably caused by, verified mitral stenosis are reported.

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TERMINAL CARDIAC MECHANISM IN CORONARY ARTERY DISEASE*

Report of Two Cases

Ben E. Goodrich, M.D., Detroit, Mich., and Robert J. Needles, M.D., St. Petersburg, Fla.

IN NOVEMBER, 1938, Grieco and Schwartz[1] demonstrated that ventricular standstill may be the cause of death after acute coronary artery thrombosis. They did not observe ventricular fibrillation following the ventricular tachycardia which preceded cardiac death. In June, 1939, F. Janney Smith[2] reported, from this clinic, a case in which ventricular fibrillation occurred after acute coronary artery thrombosis. It has been our singular experience to observe electrocardiographically, during one afternoon, the terminal cardiac mechanism in two instances of sudden death from coronary artery disease. One of these deaths was shown, at autopsy, to have been caused by marked coronary artery sclerosis (the patient had had angina pectoris). The other was undoubtedly the result of infarction of the anterior wall of the heart; it occurred on the tenth day following the coronary occlusion.

CASE REPORTS

Case 1.—A. J. A. (No. 79986), a white man, 46 years old, was first seen in June, 1926. On subsequent occasions, in the hospital and outpatient department, he had been treated for a number of minor complaints. No serious illness was noted until Aug. 2, 1939, when he stated that for several weeks he had had severe, aching pain in both shoulders and down both arms. The distress was periodic and would last only a few minutes. It was present only during exertion, and was relieved promptly by rest. It was most likely to occur after meals. There had been no substernal or precordial distress.

On Aug. 11, 1939, abut 3:00 P.M., the patient made one of his regularly scheduled visits to the outpatient department. He had been feeling well and had noted no distress or discomfort that day. In the lobby of the hospital he collapsed, became unconscious and cyanotic, and shortly vomited. He was brought to the cardiac clinic, where he recovered for a few moments and indicated that he was having crushing substernal pain. Concentrated glucose solution (100 c.c. of 20 per cent), with 3.5 grains (0.25 gram) of aminophyllin, was administered intravenously. He soon lapsed into complete coma. The ashen cyanosis increased. The cardiac rate was 54, and the beating was regular. The blood pressure could not be obtained, and the peripheral pulse was imperceptible. He was sweating profusely. An electrocardiogram was obtained. He was given 0.5 c.c. of adrenalin subcutaneously, and heat was applied externally. A pronounced protodiastolic gallop rhythm was present, together with irregularly occurring extrasystoles. The electrocardiograph was again connected. At about 3:15 P.M. a severe clonic convulsion occurred, and respirations ceased. The heart sounds could not be heard, and it was felt that the patient was dead. Artificial respiration was applied, and 1 c.c. of adrenalin was injected into the heart. No further evidence of life appeared except in the electrocardiogram (Fig. 1).

*From the Department of Medicine, Henry Ford Hospital.
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After 3:15 P.M., when, from the clinical standpoint, the patient was dead, the record first showed an almost regular heartbeat, at a rate of approximately 150, and complexes which varied slightly in contour. Three minutes later the complexes were smaller and varied more. At 3:20 and 3:21 there were prominent, rounded waves which occurred at a rate of 72; they were preceded and followed by very small deflections. At 3:22, there was, for a time, no evidence of ventricular activity, for

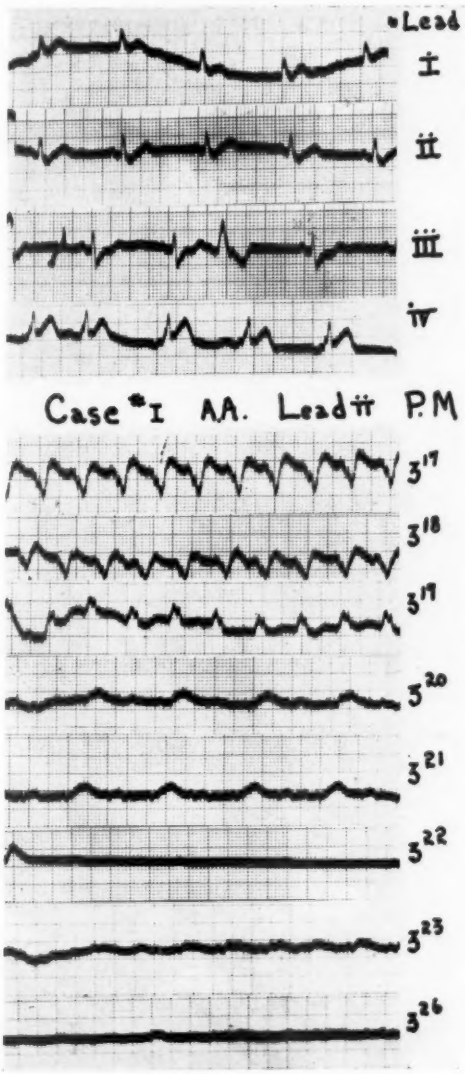

Fig. 1.

the small deflections which occurred at a rate of less than sixty a minute may have been entirely of auricular origin. With the resumption of ventricular activity, at 3:23, although the voltage was small, there continued to be a recurring similarity in the form of the complexes. The last portion of the record showed a further decrease in the amplitude of the deflections.

The autopsy was performed by Dr. G. B. Kerr. The left anterior coronary artery was tortuous and thickened, and the lumen was almost obliterated in several places by confluent atherosclerotic plaques. No fresh thrombus could be seen. The right coronary artery showed only an occasional patch of atherosclerosis. No area of myocardial infarction could be demonstrated, either grossly or by histologic section.

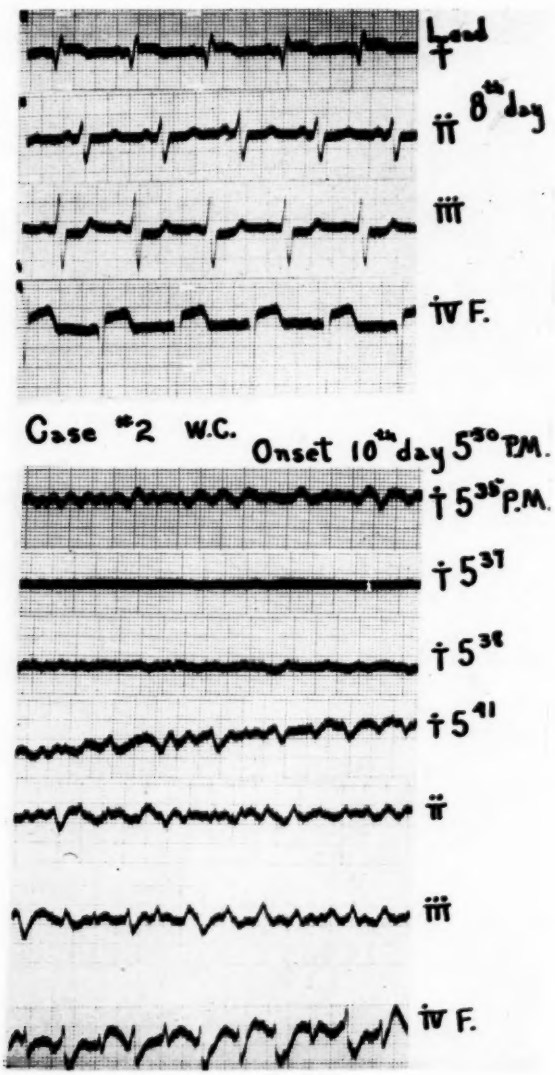

Fig. 2.

Department of Reviews and Abstracts

Selected Abstracts

Hoyos, Jorge Meneses, and Palacios, Hector Caraza: Experimental Studies on the Action of Ascorbic Acid on the Heart. An. Inst. de Biologia **10**: 173, 1939.

A solution of ascorbic acid, 1:1,000, produced increased amplitude and frequency of the heart of the turtle and the frog.

Ascorbic acid has no action upon the isolated turtle's heart other than perhaps that of producing a slight increase in the amplitude of the auricular beats.

In experimental scurvy there is a diminished voltage in the electrocardiogram; cure results in return to normal voltage.

The voltage of the normal human electrocardiogram can be increased by intravenous injection of small doses of ascorbic acid. The same can be done with stimulating doses in the rabbit. Toxic doses cause a diminution of voltage.

The effect appears to be directly on the ventricle.

JENSEN.

Maldonado-Allende, Ignacio, Orias, Oscar, and Segura, Angel S.: Attempts to Register Cardiac Sounds During Experimental Ventricular Fibrillation. Actas y Trabajos del VI Congreso Nacional de Medicina, Cordoba, vol. I, 1939.

Twenty-two dogs were used for the experiments. Their hearts were exposed and electrocardiograms and audiograms of the regular action were obtained. The ventricles were then made to fibrillate, and the fibrillation was recorded by electrocardiograms. The audiogram showed vibrations of a frequency which classed them as sound waves. The findings, however, were not as constant as the authors could wish, and the amplitude of the waves varied from moment to moment. In some cases in which the auricles continued to beat regularly, the waves indicating auricular activity continued as before. When they also fibrillated, they gave rise to waves similar to those produced by the ventricles. It is suggested that such researches may throw some light on the origin of the heart sounds.

JENSEN.

Bloomfield, Arthur L.: Dysphagia With Disorders of the Heart and Great Vessels. Am. J. M. Sc. **200**: 289, 1940.

Dysphagia may occur in connection with the following disorders of the heart and aorta: dilated left auricle, pericarditis, saccular aneurysm, dissecting aneurysm, and anomalous aortic arch.

While pressure on the esophagus is common with all of these conditions, clinical dysphagia occurs very rarely except with saccular aneurysm and anomalous aortic arch.

Difficulty in swallowing in a patient with pericarditis suggests a large effusion.

Marked dysphagia with aneurysm suggests a false sac or huge lesion with threatened rupture.

Dysphagia in a supposed case of coronary occlusion should arouse suspicion of dissecting aneurysm.

The literature dealing with the above conditions is reviewed, and a case of dysphagia associated with compression of the esophagus by an enlarged left auricle is reported.

AUTHOR.

Coelho, Eduardo, deCosta, Filipe, and deOliveira, Artur: Novocaine Infiltration of the Stellate Ganglion in Angina Pectoris. Impressa Medica. 5: 3, 1939.

The authors submitted patients with angina pectoris to exercise tolerance tests (stair climbing). They studied the effect both on the pain and on the electrocardiogram. In 70 per cent of their cases there were electrocardiographic changes following effort; these changes did not necessarily coincide with the onset of pain. Nine patients had bilateral injections of novocain into the stellate ganglion; seven had it in the left side only. In each case the injection was followed by Claude-Bernard-Horner syndrome. A control series of normal persons were similarly injected, and their electrocardiographic response to effort was tested before and after injection. Neither effort nor injection had any effect on the electrocardiogram. In the patients with angina pectoris the blocking of the ganglion prevented the pain, but it did not change the electrocardiographic response. The authors concluded that the operation only interrupted the painful sensations, but had no effect on the coronary circulation. Believing that angina pectoris is caused by coronary vasoconstriction, they assumed that the operation did not interfere with the vasoconstrictors. The operation did not delay the onset of fatigue which formerly had stopped the patients, nor did it enable any of them to climb more steps.

JENSEN.

Sodeman, William A., and Engelhardt, Hugo T.: A QRS Pattern of Diagnostic Value in the Electrocardiogram. Am. J. M. Sc. 200: 337, 1940.

A QRS pattern is described which has been found to occur in tracings from patients with heart disease in the absence of any other electrocardiographic evidence of heart disease. It promises to be of value in electrocardiographic interpretation.

AUTHORS.

Puddu, Vittorio: On the Duration of Cardiac Systole During Hypocalcemia. Boll. e atti della R. Academia medica di Roma. 64: 131, 1938.

In two cases of hypoparathyroid hypocalcemia the author found that systole as measured by the electrocardiogram was prolonged as compared with normal. This difference was not demonstrable with the sphymograph.

JENSEN.

Mussafia, A., and Puddu, V.: Electrocardiographic Researches With Multiple Thoracic Leads. Boll. e atti della R. Acedemia medica di Roma 64: 277, 1938.

Authors examined twenty-eight subjects, with the exploring electrode on various points of the precordium and with the indifferent electrode always in the left leg.

Four positions were selected: the fourth left interspace near the sternum, the apex beat, a point midway between the two at the level of the apex beat in the anterior axillary line, and the midaxillary line.

They conclude that the electrocardiogram depends on the size of the heart and its position within the chest. It is determined by the potential of the adjoining part of the heart. The less the distance of the heart from the electrode, that is, the closer the heart is to the chest wall, the more circumscribed is the surface of the heart which affects the electrode. These two statements are confirmed by numerous other researches.

JENSEN.

Mussafia, A., and Puddu, V.: Results of Two Precordial Leads. Cuore e circolaz. **23**: 281, 1939.

In 500 tracings on 400 patients, two precordial leads were compared, one with the exploring electrode on the fourth intercostal space at the parasternal line (CF_3), and the other with the exploring electrode at the apex lead (IV F). In both, the indifferent electrode was on the left foot.

Lead IV F is more specific and more sensible than CF_3, when the general cardiac state is considered. However, in some patients with heart disease, CF_3 alone was affected; especially in some cases of myocardial infarctions was the electrocardiographic change present only in CF_3.

The authors recommend the use of both precordial leads together, at least when coronary thrombosis is suspected.

JENSEN.

Coelho, Eduardo, and deOliveira, Artur: Tachycardia and Paroxymal Ventricular Fibrillation in Infarction of the Myocardium. Cardiologia **3**: 169, 1939.

Three case reports of ventricular tachycardia and one of ventricular fibrillation following cardiac infarction are given. The attacks were of unusually long duration and occurred in younger patients (aged 45, 40, and 38 years). The article is accompanied by numerous electrocardiogram tracings.

AUTHORS.

Davis, John S., Jr.: Diagnosis and Treatment of Gonorrheal Septicemia and Gonorrheal Endocarditis. Arch. Int. Med. **66**: 418, 1940.

Gonorrheal endocarditis is a fairly common disease. The diagnosis can and should be made early so that proper treatment may be instituted. Since a positive blood culture is frequently hard to obtain and is not the only diagnostic criterion, it is not absolutely necessary, and it may be dangerous to delay the diagnosis for lack of this one determination. The high percentage of diagnoses made at autopsy bears mute testimony to this. The high mortality should, in the future, be curtailed and the majority of the patients should recover.

AUTHOR.

Rosenberg, David H.: Bacterial Endocarditis and Syphilis of the Aortic Valve. Arch. Int. Med. **66**: 441, 1940.

The literature dealing with bacterial endocarditis and syphilitic valvular disease is critically reviewed, and the reported cases are grouped categorically as proved, doubtful, and unproved.

Since Libman first directed attention to the infrequent concurrence of these diseases, only ten proved cases have been reported. To these, the records of seven more instances are added, making a total of seventeen proved cases. Of the remaining cases in the literature, four are regarded as doubtful, and in twenty-nine the existence of syphilitic aortic valvular disease remains unproved.

Based on the available data, a study of the incidence is made, and the suggestions offered for the interpretation of the rarity of this combination are discussed. Attention is drawn to the diagnostic difficulties and to the limitations of a positive Wassermann reaction.

Contrary to the opinions expressed in current literature, it is apparent from this study that bacterial endocarditis associated with syphilitic aortitis per se (without involvement of the aortic cusps or commissures) is not of rare occurrence.

With greater interest directed to the clinical and anatomic recognition of bacterial endocarditis superimposed on syphilitic valvular deformities, it is likely that their coexistence may be observed more frequently than heretofore.

AUTHOR.

Gauld, Ross L., and Read, Frances E. M.: Studies in Rheumatic Disease. V. The Age at Onset of Primary Rheumatic Attack. J. Clin. Investigation **19**: 729, 1940.

Various defects in published data relative to the age selection of rheumatic disease are discussed, and the results of a study on this subject, in which every effort was made to eliminate these errors, are presented.

The group for study was a generation of families of ninety-six consecutive patients admitted to the Cardiac Clinic of the Harriet Lane Home because of rheumatic disease, and it consisted of parents, uncles, and aunts of these patients (index cases).

The accuracy of the data and various possible errors in the histories are recognized and discussed.

The age at onset of 115 cases of rheumatic disease occurring in the generation was found to fall most frequently between the ages of 5 and 14 years, and 25 and 34 years.

The relative risk of developing the disease was determined by dividing the number of onsets at each age by the person-years at risk for the corresponding age to obtain an annual incidence rate. This risk was found to be greatest between the ages of 5 and 14 years and 25 and 34 years.

AUTHORS.

Coelho, Eduardo, and deOliveira, Artur: Syphilis of the Interventricular Septum and Ventricular Tachycardia; Syphilis of the Pulmonary Artery. Arch. d. mal. du Coeur **32**: 17, 1939.

This report of a gumma in the interventricular septum is the second case of the kind reported in the literature. The patient, aged 24 years, died from heart failure and A-V block and defective intraventricular conduction. At autopsy there were shown syphilitic changes in the pulmonic valves and in the pulmonic artery. There were also gummas in the interventricular septum.

This case is of exceptional interest.

JENSEN.

Bruck, Max: Is There a Physiologic Hypertonia of the Aged? Cardiologia **4**: 165, 1940.

The author examines the question whether there is a physiologic arterial hypertension in old age and whether the increased blood pressure in old age is a sign of disease.

The blood pressure levels, studied in healthy students of athletics, fluctuate according to Gaus' curve.

The figures in older people do not conform to the Gaus' curve and there is no evidence for increased physiologic fluctuations. The observations can be interpreted as a mixture of the normal curve with pathologic figures; thus, it is impossible to deduce a physiologic increase of the arterial blood pressure in old age from these observations.

There is no evidence for a physiologic increase in arterial pressure in old age. There is evidence for the view that the pressure remains stationary or may even decrease.

The probability for the fluctuations of arterial pressure in normals is calculated. The probability is small that a pressure of 150 mm. Hg falls within the range of the normal.

AUTHOR.

de Navasquez, S., Forbes, J. R., and Holling, H. E.: Right Ventricular Hypertrophy of Unknown Origin: So-called Pulmonary Hypertension. Brit. Heart J. 2: 177, 1940.

Three cases of severe right ventricular hypertrophy of unknown origin have been described.

The usually accepted causes of such hypertrophy due to disease of the heart and lungs have been excluded.

The clinical and pathologic changes have been described and discussed.

It is suggested that the term "idiopathic right ventricular hypertrophy" should in future replace "primary pulmonary arteriosclerosis" or "hypertension," which have no foundation in fact.

AUTHORS.

East, Terence: Pulmonary Hypertension. Brit. Heart J. 2: 189, 1940.

Three cases are described in which failure of a conspicuously hypertrophied right ventricle took place. At autopsy no satisfactory cause for this hypertrophy could be found.

They present a clinical picture which should be fairly easily recognizable during life.

1. Enlargement of the right ventricle, with the characteristic electrocardiogram.
2. Enlargement of the pulmonary artery, confirmed by the skiagram.
3. A loud pulmonary second sound suggesting a high pressure in it.
4. Intractable and progressive failure of the right ventricle, with the maintenance of normal rhythm, dyspnea of any severity being absent.
5. A normal appearance of the left auricle.
6. An absence of valvular defects, congenital or acquired, or of patent septa. (Patent interauricular septum might be difficult to exclude.)
7. An absence of pulmonary disease.
8. The absence of evidence of syphilis.

It is suggested that a condition of idiopathic or essential pulmonary hypertension may exist as a cause for those findings.

AUTHOR.

Armstrong, T. G.: Failure of the Right Ventricle. Brit. Heart J. 2: 201, 1940.

It is suggested, that the duration of the failure and its unremitting nature in this case were due to the right ventricle failing alone. The unusual pathologic findings, the cardiac "cirrhosis" of the liver, and the chronic indurative changes in the peritoneum, were probably an expression of the extreme chronicity of the disease, and are strictly comparable with the findings in constrictive pericarditis.

AUTHOR.

Schiappoli, Franco: On the Significance of Venous Pressure Registered by Clinical Methods. IV. Modification in Normal Subjects Following Reflex Stimulation, Thermal and Mechanical. Cardiologia 4: 214, 1940.

Changes of venous pressure following thermal and mechanical stimulation and after pressure on the carotid sinus and the eyeball were studied. Changes were observed which were independent of variations of arterial pressure with regard to duration, extent, and direction. Considerable changes were observed following stimulation which produced definite parasympathetic excitation.

The determining factor influencing venous pressure is the tone of the veins. Changes in venous pressure can be produced only by reflexogenous modifications.

AUTHOR.

Robinson, S. C., and Brucer, Marshall: Body Build and Hypertension. Arch. Int. Med. **66**: 393, 1940.

A review of the literature shows that no rigidly controlled statistical study on a sufficiently large series has conclusively established a positive correlation between blood pressure and body build. Some writers contend that no correlation whatsoever exists.

In this study of blood pressure and body build, made on 3,658 persons, an index derived from dividing the chest circumference by the standing height was used as a ratio of width to height to distinguish the narrow linear type of persons from the broad lateral type.

Among 1,861 men and 1,797 women, 17 per cent of the men and 31 per cent of the women were of the narrow-chested, linear type of build, and 12 per cent of both men and women were of the broad-chested, lateral build.

Observations lead both to the general conclusion that a positive correlation between body build and blood pressure does exist and to the following specific conclusions:

In both men and women there is an increase in the average build—chest-to-height ratio—with an increase in age. This increase in the adult is greatest before the age of 50 years; after this age there is a tendency for the average build to decrease.

Men and women of lateral, or broad, build show a marked tendency to hypertension. The mean, median, and modal systolic and diastolic blood pressures increase with an increase in chest-height ratio.

The lateral, broad-chested type of man has more than four times the expectancy of development of diastolic hypertension as has the man of linear, or slender, build. The women of lateral build have almost eleven times the expectancy of development of systolic hypertension and eight times the expectancy of diastolic hypertension as have the women of linear build.

The men and women of lateral build have only about one-half the expectancy of a low systolic or diastolic pressure as have men and women of the linear build.

In any random group of men of lateral build, high systolic and diastolic pressures occur three times as often as low pressures. In any random group of women of lateral build, the ratio of high systolic pressure to low systolic pressure is 5:1, and the ratio of high diastolic pressure to low diastolic pressure is 4:1.

In any random group of men of linear build, the ratio of low systolic pressure to high systolic pressure is 3:1, and the ratio of low diastolic pressure to high diastolic pressure is 5:1. In the group of slender women the ratio of low to high systolic or diastolic pressures is 4:1.

In any random group of persons with systolic hypertension the ratio of lateral to linear builds will be: men, 4:1; women, 11:1. In any random group of persons with diastolic hypertension the ratio of lateral to linear builds will be: men, 7:1; women: 8:6.

In any random group of persons with low systolic pressures the ratio of linear to lateral builds for both men and women will be greater than 2:1. In those with low diastolic pressure the corresponding ratio for men will be greater than 2:1, and for women, almost 2:1.

The relation between lateral build and hypertension and between linear build and low blood pressure is found in all age groups.

The incidence of high pressures increases and that of low pressures decreases with age in men of lateral build. In those of linear build the incidence of high pressure is constant up to the seventh decade; the incidence of low pressure is constant throughout life.

The incidence of high pressures increases with age more markedly among women of lateral build than among those of linear build, and at every age the incidence of low pressure is greatest among the women of linear build.

AUTHORS.

Williams, J. R., Jr., Grollman, Arthur, and Harrison, T. R.: The Reduction of the Blood Pressure of Hypertensive Dogs by the Administration of Renal Extract. Am. J. Physiol. **130:** 496, 1940.

A series of eighteen hypertensive dogs were treated with renal extracts. The blood pressure of these animals was reduced appreciably, normal values being attained in some cases. Severe untoward symptoms accompanied this reduction in many cases. The bearing of these findings on certain aspects of the problem of renal hypertension has been discussed.

AUTHORS.

Wakerlin, G. E., and Gaines, Walter: The Effect of Various Agents on the Blood Pressure of Renal Hypertensive Dogs. Am. J. Physiol. **130:** 568, 1940.

Estrone, testosterone, and extracts of liver, pancreas, and garlic and parsley had no significant effect on the blood pressures of renal ischemic hypertensive dogs.

Temporarily, dog renin slightly but significantly increased the blood pressures of renal hypertensive and normal dogs.

Fresh hog kidney, adrenal cortical extract, whole pituitary extract, and pituitrin were without effect on the blood pressure in experimental renal hypertension in dogs.

Distemper lowered the blood pressures of renal hypertensive dogs but extensive cellulitis was without effect.

The growing evidence of similarity between experimental renal ischemic hypertension in the dog and essential hypertension in man is further substantiated.

AUTHORS.

Maldonado-Allende, Ignacio: Influence of Tobacco on Arterial Hypertension. Actas y Trabajos del VI Congreso Nacional de Medicina, Cordoba, Vol. II, 1939.

The author analyzed the effect of tobacco smoke on twenty-four patients with arterial hypertension, who were smokers and nonsmokers; he tested the effect on the heart rate, the blood pressure, and the electrocardiogram.

Heart rate and blood pressure showed no significant changes. The electrocardiogram showed transient changes in the T waves in some or in all leads, in a high percentage of cases. These changes occurred more frequently in patients with hypertension. The changes are explained by (1) direct toxic effect on the myocardium, (2) indirect toxic effect via the nervous system, (3) production of chemical changes in the blood, slight, but still sufficient to influence cardiac nutrition, (4) constriction of the coronary arteries by the tobacco.

It is thought that this effect regularly produced on the smoker's heart may eventually result in permanent cardiac damage.

JENSEN.

Scaffidi, Vittorio, Jr., and Positano, Giuseppe: On the Significance of Venous Pressure Registered by Clinical Methods. V. On the Existence of Reflex Venous Zone in the Region of the Superior Vena Cava. Cardiologia 4: 235, 1940.

Mechanical stimulations of the preauricular region of the inferior vena cava in dogs with closed chest produced hypertension in these zones; stimulations of the superior vena cava lower the pressure in the region of the superior vena cava. These fluctuations of venous pressure are due to reflexes which regulate the venous circulation.

AUTHORS.

Keil, Harry: Dermatomyositis and Systemic Lupus Erythematosus. I. A Clinical Report of "Transitional" Cases, With a Consideration of Lead as a Possible Etiologic Factor. Arch. Int. Med. 66: 109, 1940.

The protocols of five cases are recorded in detail in order to depict the varied manifestations of dermatomyositis as well as to illustrate what may be called a condition "transitional" between that disease and systemic lupus erythematosus. Additional examples of this condition are mentioned only in connection with the elaboration or substantiation of certain points. A preliminary attempt is made to clear the ground for a more detailed consideration of the similarities and the differences in the clinicopathologic features exhibited by each of these diseases in their typical forms.

Two instances of dermatomyositis are described, one very briefly, in which there appeared suggestive evidence that the factor of lead played an important part in the evolution of the clinical picture. These cases are not isolated and are considered in relation to the data indicating that this heavy metal is a vascular poison, especially in certain susceptible persons. These data are carefully reviewed, notably because there is a tendency on the part of observers to attribute various disease to lead absorption; whenever such views are advanced, critical investigators have, with considerable justification, refused credence to them. Moreover, the cases under my observation did not present the classic evidence of plumbism. Nevertheless, it is suggested that lead may exert a deleterious effect on the blood vessels in especially susceptible persons with a presumably unstable vascular system, and in such persons "vascular disease may be and remain the solitary sign of lead poisoning." The connection between this heavy metal and vascular disease is regarded as probable, even though specific or pathognomonic lesions are not produced. The evidence compiled in this paper cannot be summarily dismissed without further investigation of the problem, which is admittedly difficult.

AUTHOR.

Keil, Harry: Dermatomyositis and Systemic Lupus Erythematosus. II. A Comparative Study of the Essential Clinicopathologic Features. Arch. Int. Med. 66: 339, 1940.

This study is concerned with a comparative analysis of the essential clinicopathologic features presented by systemic lupus erythematosus and dermatomyositis. Among the clinical phenomena encountered in both diseases are fever, pains generally regarded as articular, similar cutaneous and oral lesions, sensitivity to sunlight, Raynaud-like symptoms, lymphadenopathy, splenomegaly, leucopenia, tendency to purpura, alopecia of the scalp, sterile cultures of blood, muscular involvement, and renal disease. At times both diseases may also run an afebrile course, and the clinical picture may occasionally be dominated by what may be called the sequelae of these conditions. Despite these similarities and the occasional overlapping of features, the average typical example of each disease runs a fairly distinctive course. The main body of the paper is devoted to an analysis of the differences in the clinicopathologic attributes. These are studied under the following headings: (1) age, sex, and seasonal incidence, (2) cutaneous lesions, (3) disease in the muscles, (4) involvement of subcutaneous tissue, (5) articular involvement, (6) renal disease, (7) ophthalmoscopic observations, (8) cardiac involvement, (9) disease in the serous membranes, (10) anomalies of the lymph nodes, (11) involvement of the spleen, (12) disease in the liver, and (13) involvement of the brain. Certain laboratory data are also compared. Likewise, differences in the prognosis are briefly discussed. Finally, the pathologic data thus far available are subjected to a critical examination with respect to their significance for diagnosis, and an effort is made to expose some of the many problems encountered in the evaluation of such observations.

AUTHOR.

Bowers, James M.: Arteritis of the Temporal Vessels. Arch. Int. Med. 66: 384, 1940.

Report of a case of inflammation of the temporal arteries is presented. For a considerable period before diagnosis the associated headache was attributed to severe arterial hypertension. Undoubtedly, the occipital arteries were involved in a similar inflammatory process at the same time. Nine months after the subsidence of signs and symptoms, the patient suffered a cerebral vascular mishap, which probably was due to arteritis of the cerebral vessels, of the same nature. Interruption of the pain pathway of the sympathetic nervous system after resection of an arterial segment and injection of vitamin B_1 produced relief from pain. Many points in favor of designation of this condition as a separate entity of arteritis, especially of its distinction from periarteritis nodosa, may be found in the reports of the sixteen cases now on record.

AUTHOR.

Patek, Arthur J., Jr., Post, Joseph, and Victor, Joseph C.: The Vascular "Spider" Associated With Cirrhosis of the Liver. Am. J. M. Sc. 200: 341, 1940.

The vascular spider, associated with disease of the liver, has the physiologic characteristics of an artery. This has been demonstrated by studies on direction of blood flow, pulsations, contractility, intravascular pressure, nad pharmacologic reactions.

In serial sections, the histologic characteristics of two lesions are those of an artery and its arteriolar branches. In five others they resemble, in a magnified form, the arterial segment of an arteriovenous anastomosis (glomus). However, the branches of these vessels are continued into capillaries and are not directed into veins.

AUTHORS.

Lippincott, Stuart W.: Abdominal Aortic Mycotic Dissecting Aneurysm. Canad. M. A. J. 43: 115, 1940.

This is a case report of an abdominal aortic aneurysm in which the gross examination did not reveal the nature of the process. Detailed microscopic studies showed both arteriosclerosis and syphilis although they were not the underlying factors in the dissecting aneurysm. The formation of this resulted from a septic medial necrosis. There was a complicating infection in the ear and the right knee joint, containing ß-hemolytic streptococci. These organisms were responsible for the production of the aortitis, with medial necrosis, intimal rupture, and formation of this rare form of dissecting aneurysm.

MCCULLOCH.

Porter, William B., and Vaughan, Edwin W.: Coronary Embolism: A Complication of Syphilitic Aortitis. Am. J. M. Sc. 200: 184, 1940.

Thirty cases of coronary embolism are analyzed as to age, sex, source of embolus, branch of the coronary artery occluded, and type of death. Three new cases of coronary embolism are reported, all of which occurred in colored males. Syphilitic aortitis was the indirect source of the embolus in each case.

AUTHORS.

Weiss, Soma, Kinney, Thomas D., and Maher, Mary M.: Dissecting Aneurysm of the Aorta With Experimental Atherosclerosis. Am. J. M. Sc. 200: 192, 1940.

Three cases of healed and functioning dissecting aneurysm are reported. Endothelium and atherosclerosis developed over the internal surface of the new aortic

channel. The atherosclerosis of the dissected aortic wall was pronounced in one of the cases and mild in two. In none of the cases did the existence of a double-channeled aorta contribute to the death of the patient.

In a 73-year-old female, with a healed dissecting aneurysm, the roentgen-ray picture revealed a double shadow corresponding to the double-channeled aorta. The surface of the new aortic channel was covered with numerous atherosclerotic plaques and endothelial islands.

In Case 2 endothelialization and mild atherosclerosis of the dissecting aneurysm developed within twenty-three months.

The histologic structure of the parallel strands bridging the lumen of the new aortic channel indicates an origin from the frayed-out strands of elastic from the media, rather than intercostal arteries.

In approximately 10 per cent of the reported cases, dissecting aneurysm heals, is not the cause of death, and can be compatible with adequate functional capacity for years.

AUTHORS.

Gross, Harry, and Philips, Benjamin: Complete Occlusion of the Abdominal Aorta. Am. J. M. Sc. **200:** 203, 1940.

Seven cases of complete occlusion of the aorta at its bifurcation, observed during the course of 5,350 autopsies, are presented.

Of these, four were patients with atherosclerosis of the coronary arteries and aorta, two with diffuse vascular disease involving the venous system, and one with chronic rheumatic cardiovalvular disease, auricular fibrillation, and a ball-valve thrombus of the left auricle.

Clinically, the classical picture usually associated with complete occlusion of the aorta at its bifurcation occurred in one case. In the remaining six, the clinical variations were probably due to: (1) differences in the rate of progression of the occlusion; (2) the presence of an adequate collateral circulation; and (3) subsequent development of a more efficient anastomotic circulation.

In two cases of peripheral arteriosclerosis, a rapid and progressive course with early bilateral involvement and the recurrence and progression of gangrene of the stump should have suggested the existence of an associated occlusive lesion of the aorta.

The difficulties inherent in making the differential diagnosis between thrombosis and embolism as the cause of complete occlusion are discussed.

AUTHORS.

Follis, Richard H., Jr.: The Coronary Arteries in Relation to Sudden Death During Anaesthesia. Bull. Johns Hopkins Hosp. **47:** 211, 1940.

Three cases of sudden death during nitrous oxide, oxygen and ether anesthesia are presented. In two of them the right coronary orifice was very small, and the circumference of the right coronary artery was only one-half that of the left. In the third case there was extensive arteriosclerosis. These cases seem to re-emphasize the importance of the status of the coronary arterial system in relation to sudden death during anesthesia.

AUTHOR.

Gregg, Donald E., and Green, Harold D.: Registration and Interpretation of Normal Phasic Inflow Into a Left Coronary Artery by an Improved Differential Manometric Method. Am. J. Physiol. **130:** 114, 1940.

A method is described for continuous optical registration of the instantaneous rate of inflow into a coronary artery. This involves shunting the blood from the

aorta to the coronary artery through a short external circuit containing an orifice (or other device) connected with a differential manometer.

The left coronary inflow curves so obtained demonstrate that beginning approximately at the onset of isometric contraction there is a rapid retardation of flow but that with the rise of aortic pressure during ejection the inflow rapidly accelerates, reaching a peak during the middle of the rise of aortic pressure and then declining to a more or less constant rate of inflow during the latter part of systole. Following the incisura there is again a rapid acceleration, the inflow reaching a peak early in diastole and then declining with the progressive fall of aortic pressure in diastole.

The inflow records are complicated by volume elastic effects due to the cyclic rise and fall of aortic pressure and by a compressor action of ventricular systole.

Despite these complications, and unless some other unknown factors are operating, it seems probable that the rate of inflow at the end of diastole, just preceding isometric contraction, can be used as an index of intramural flow during diastole.

Similarly it seems probable that the rate of inflow during the brief interval at, or just preceding, the onset of protodiastole, i.e., at the peak of the peripheral coronary pressure curve, can be used as an index of the systolic rate of intramural flow. In almost all instances the systolic intramural flow so measured is of sizable magnitude.

The rate of intramural flow per millimeter of differential pressure is greater during systole than during diastole.

Simultaneous measurement of aortic pressure and rate of intramural flow indicates that the resistance to blood flow existing during the latter part of diastole is increased from 2- to 4-fold during systole.

The total flow may be determined from the moment-to-moment flow curve by appropriate procedures.

AUTHORS.

Brightman, I. Jay, and Batterman, Robert C.: The Treatment of Edema by Rectal Administration of Diuretics. J. Lab. and Clin. Med. 25: 1038, 1940.

The mercurin and modified salyrgan suppositories produce only minimal changes in the rectal mucosa, but they may occasionally cause local discomfort and burning.

Mercurial diuretic suppositories may produce a definite and clinically effective diuresis, but their dependability is only 60 per cent.

The possible danger of administering a mercurial diuretic intravenously soon after a suppository is discussed.

AUTHORS.

Robertson, Harold F., and Faust, Frederick B.: Theophylline with Isopropanolamine in Heart Disease. With Especial Reference to Congestive Failure. J. Lab. and Clin. Med. 25: 1066, 1940.

The effect of theophylline with isopropanolamine was studied in a series of twenty-one patients, with reference to capillary dilatation, arterial, venous, and spinal fluid pressures. These pressures showed a definite fall associated with a capillary dilatation. This response to the drug, although comparatively brief, may prove useful in the treatment of congestive heart failure in conjunction with venesection and other appropriate measures. Further study may establish a more sustained effect with the oral or intramuscular administration of this preparation. Our observations showed considerable relief from dyspnea and orthopnea shortly

after injection, lasting from three to four hours. The clinical improvement was far more sustained than the laboratory studies indicate.

AUTHORS.

Kissane, R. W., and Koons, R. A.: Spontaneous Redigitalization Following Rapid Diuresis in Congestive Heart Failure. Tr. Am. Therap. Soc. 29: 111, 1940.

Forty-three cases of postdiuretic syndrome have been observed; some occurred accidentally and others were produced experimentally. The chief symptoms are marked bradycardia, nausea, vomiting, headache, weakness, extrasystoles, and coupled rhythm. Occasional transient auricular fibrillation or flutter will occur.

The primary factor in the production of this syndrome appears to be the reabsorption of digitalis substances from the edematous fluids; the secondary factor, the rate of elimination of this fluid through the kidneys with sufficient rapidity to prevent the elimination of these substances. It appears that both these factors must be present before the syndrome will occur. The syndrome does not appear to be due to mercurial diuretics since it occurred following rapid diuresis with glucose.

It is suggested that diuresis be produced slowly and digitalis be stopped until the amount of the reabsorption can be determined.

AUTHORS.

Starr, Isaac, and Ferguson, L. K.: B Methylcholine Urethane: Its Action in Various Normal and Abnormal Conditions, Especially Postoperative Urinary Retention. Am. J. M. Sc. 200: 372, 1940.

Beta methylcholine urethane, a stable choline derivative synthesized by Major at the suggestion of Simonart, has been studied in the clinic.

Having the typical choline action, this drug produces effects analogous to stimulation of parasympathetic nerves. These effects can be abolished by atropine. It is more stable than mecholyl and largely lacks the undesired nicotine-like action of doryl. It is probably for this reason that uncomfortable side effects are at a minimum. The authors regard it as superior to doryl for use in the clinic.

Given to twenty-five normal young adults, in suitable dosage, the drug caused increased peristalsis and a desire to void when its action on the heart and circulation, salivation, and sweating was minimal.

The drug caused emptying of the bladder in 68 per cent of 122 patients with postoperative urinary retention, reducing the necessity for catheterization by two-thirds.

It has also been used with benefit in patients with neurogenic bladders and in certain cases of abdominal distention, extreme constipation, and peripheral vascular disease.

AUTHORS.

Book Reviews

THE SOLDIER'S HEART AND THE EFFORT SYNDROME: By Sir Thomas Lewis. Second edition, 103 pages, Shaw and Sons, London, 1940. Price, 8/6.

The first edition of this book was prepared shortly before the close of the war of 1914-1918. The book has now been drastically revised—largely rewritten, in fact. It is not a treatise on heart disease, but a collection of information which is particularly applicable to the soldier.

As in the first edition, there are four major sections: the first deals with definition, etiology, symptoms, prognosis, and treatment of the effort syndrome; the second, with the diagnosis of heart disease in soldiers; the third, with the examination of recruits; and the fourth, which is less important, with medical reports of discharged soldiers. The quality of the book is up to Sir Thomas' high standard. Facts and statements are presented briefly, clearly, and forcefully, and are obviously backed up by a wealth of information and preparation.

The trend of the times indicates the need for this new, revised edition. Although the effort syndrome is encountered among civilians, it is much more important in military practice. The section on diagnosis of heart disease in soldiers is of particular value at present, in view of this country's national defense measures. The part which the members of the medical profession will be called on to play, especially those who will examine recruits, if compulsory military training is adopted, and those who will serve as cardiac consultants, requires that this subject be handled in an intelligent, coordinated way. This book is a condensed report and guide, and should be read by every cardiologist and consultant. All of the British experience is filtered out and condensed in its few pages.

HUGH MCCULLOCH.

ELECTROCARDIOGRAPHY: By Chauncey C. Maher, M.D., Assistant Professor of Medicine, Northwestern University, and Paul H. Wosika, M.D., Instructor in Medicine, Northwestern University. Ed. 3, 334 pages, 100 electrocardiograms, 42 diagrams, 5 roentgenograms, $4.00, Baltimore, 1940, The Williams and Wilkins Company.

The appearance of this work in its third edition speaks for its popularity and also for the need of a simple exposition of the important subject of electrocardiography. The authors have adopted a novel, clear, and concise method of explanation, both of its theory and practical application. The book is essentially a primer, and, as such, is excellent. There is a clear discussion of the anatomy of the conduction system. Diagrams are drawn with many of the electrocardiograms, pointing out topographically the anatomic and physiologic condition of the heart which is responsible for the abnormal mechanism. This is especially well done in the case of auricular flutter and fibrillation. This edition has been enlarged and its scope broadened, particularly with reference to correlation of the roentgenographic appearance of the heart with the electrical axis. Perhaps subsequent editions will consider such subjects as lateral wall infarction, pulmonary infarction, hypo- and hypercalcemia, acidosis, alkalosis, and acute nephritis.

This book is recommended to the beginner in electrocardiography; he will find it a convenient stepping stone to more extensive treatises. The type, paper, and binding are excellent, and aid in making the book attractive.

HAROLD FEIL.

CLINICAL HEART DISEASE; 2nd Edition: By Samuel A. Levine, M.D., Assistant Professor of Medicine, Harvard Medical School, Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston. W. B. Saunders Co., 1940, 477 pages, 109 illustrations.

The second edition of this deservedly popular book does not incorporate many important changes from the first edition, which appeared four years ago. However, the reader is informed that no great or fundamental advances in cardiology have taken place during that period.

The author, as is well known, has been an enthusiastic and tireless student of his subject for many years. He writes tersely and clearly and is willing to express his opinions on controversial subjects. Since those opinions are the result, not of desk research, but of careful, intelligent work and observation, they cannot fail to interest even those who have labored long in similar vineyards. The book is intended for general practitioners, and fulfills their everyday needs very well indeed. It should also be helpful to cardiologists, especially those who have not as yet been through the mill of arduous clinical training.

CHARLES C. WOLFERTH.

MANUAL OF PERIPHERAL VASCULAR DISORDERS: By David W. Kramer, M.D., Assistant Professor of Medicine, Jefferson Medical College. Philadelphia, 1940, 448 pages, 126 illustrations, $6.00, The Blakiston Company.

This book attempts to give the general practitioner and the specialist in peripheral vascular disease, *first*, a careful outline of the symptoms, signs, and tests, and, *second*, a classification of the various vascular disorders, their etiology, pathology, diagnosis, and treatment. The author has succeeded in the first part in presenting an orderly method of study and in describing accurately the various symptoms and signs. His description of diagnostic apparatus and tests is complete, and he gives a very fair estimation of their value. One hundred eighteen pages are given over to this important part of the book.

Part II would be better titled "The Occlusive Arterial Disorders," instead of "The Occlusive Vascular Disorders," for diseases of the veins are barely mentioned and the lymphatics are not included. No satisfactory classification of peripheral vascular diseases has thus far been presented. The author has made an earnest attempt to accomplish this, but leaves one a little confused. For instance, in Chapter 10 he includes diabetic arteritis under chronic forms, listing it with the so-called infectious group.

Chapters 16, 17, and 18, on vasospastic diseases, could be combined, for there is some reduplication, and all of the conditions which are described are very closely related.

One is glad to see a section on hypertension in a manual of this type.

The sections on treatment are well arranged, and the various types of therapy receive excellent evaluation. The author considers the economic factors in deciding what treatment to use, and attempts to avoid elaborate apparatus unless it is definitely indicated.

Part IV is entitled "Gangrene and Disorders of the Veins." One wonders why gangrene was not placed under arterial disease, for it is of relatively little importance in venous pathology. One is also disappointed in noting only 24 pages on

veins, and, moreover, no section or chapter on lymphatic disease. The bibliographies are satisfactory and plenty of case reports are included. Some of the illustrations, such as Figs. 2 and 22, fail to show at all, or clearly, what is intended. Other photographs are quite indistinct. The addition of more photographs, especially "before and after," with the case reports would be of value.

Finally, this book is essentially a manual for the practitioner. There is little that is new for the worker in this specialty. As compared to many recent books on peripheral vascular disease, it evaluates treatment in a much more unbiased way. It is almost entirely devoted to diseases which affect the arteries primarily, and, therefore, does not completely cover the field indicated by its title.

A. WILBUR DURYEE.

ACUTE MYOCARDITIS: By F. Wuhrmann. 148 pages, S. Karger, Basel.

This monograph may be of fundamental importance. Its purpose is to give a complete picture of a neglected condition, namely, acute interstitial myocarditis, originally described by Fiedler in 1897. The work is based on an original series of thirty-six cases. This is recorded in the beginning of the book. Fifteen of the cases occurred in patients with pulmonary tuberculosis. The second half is given over to a general description. The condition is well circumscribed and may be distinguished from the changes which follow diphtheria, scarlet fever, sepsis, and rheumatism.

A review of the not very numerous cases in the literature and eighty-six illustrations, which are very clear, follow. Altogether, this is a most commendable work.

JULIUS JENSEN.

PHONOCARDIOGRAPHIC AND HEMODYNAMIC STUDIES IN PREGNANT WOMEN AND FETI DURING THE LAST MONTHS OF NORMAL PREGNANCY: By Julio C. Pereira. 114 pages, Buenos Aires, 1939.

By the direct method of Wiggers and Dean, the author recorded the phonocardiograms of forty-nine normal women and found no essential difference between these and records obtained from men. Nor did fifty pregnant women show any important difference.

The author also recorded the fetal phonocardiogram, and found that the first sound has a duration of 0.105 ± 0.0024 second, and is composed of 3.8 ± 0.088 vibrations, with an average tracing amplitude of 9.41 ± 0.348 mm. The second sound has a duration of 0.07 ± 0.0015 second, is composed of 2.59 ± 0.0539 vibrations, and has a vibration amplitude of 6.28 ± 0.1723 mm.

The author believes that these results are more accurate than the discrepant ones obtained with the Cambridge stethograph.

The average fetal heart rate was 141. The duration of systole decreases as the rate increases.

Altogether, this constitutes an elaborate and careful statistical study, richly illustrated.

JULIUS JENSEN.

STUDIES ON VENOUS PRESSURE DURING VALSALVA'S EXPERIMENT: By Knut Liedholm. Acta med. Scandinav., 213 pages, Suppl. 106 (Lund), 1939.

This is a most detailed and elaborate analysis of Valsalva's experiment, with special study of the venous pressure. The author justifies his effort by stating that Valsalva's experiment is by no means exclusively a laboratory test, but a mechanism which functions with every sudden muscular effort. In view of the attention which recently has been paid to venous pressures in general, this behavior during Valsalva's experiment may be important. The author then analyzes the nature of Valsalva's

experiment and the literature on its effect on the circulation: the size of the heart, stroke and minute volume, arterial pressure and venous pressure, heart rate, and changes in the capillaries.

The author then describes his elaborate technique for the simultaneous kymographic registration of thoracic and abdominal breathing and venous and arterial pressure. The methods for measurement of these phenomena are then elaborately discussed.

The author has subjected twenty-nine persons with normal cardiovascular systems, twenty-eight with hypertension, and forty-five with valvular lesions of the heart to his experiments. In the analysis of his observations, relatively slight emphasis has been placed on the state of compensation of the patient.

There is an elaborate analysis of the effect of respiration on the venous pressure; in some persons the venous pressure sinks during inspiration, and in others it rises. The reason for this discrepancy is not clear.

The increase in intrathoracic pressure during Valsalva's experiment is often followed, in a few seconds, by an increase in venous pressure which continues gradually until a certain maximum is reached. In extreme cases this may reach 71 cm. of H_2O. The curve proceeds at the same rate of incline till the top is reached. When the intrathoracic pressure is released, the venous pressure again falls at an even rate until it approaches the normal level, when it gradually flattens out. This function is then submitted to a most complete and elaborate mathematical analysis. Taken as groups, the normal persons showed the highest increase in venous pressure, those with valvular lesions the second highest, and those with hypertension the poorest response. This difference Liedholm ascribes to lowered vital capacity, i.e., impaired compensation; yet he does not enter further into the relation. He does not consider Valsalva's experiment suitable for a test of cardiovascular function. The decrease in venous pressure is largely influenced by respiration. A great many curves and statistical tables are included in the work. There are finally, a summary in English and ten pages of references.

With the exception of the relation of Valsalva's experiment to decompensation (which I should consider of some importance), this work leaves little to be said about Valsalva's experiment. The references appear to cover all essential literature on the venous pressure.

JULIUS JENSEN.

LA CIRCULATION DE RETOUR: By André Jouve and Jean Vague, 180 pages, no illustrations, 1940, Masson et Cie., Paris.

The title of this monograph cannot be translated directly into English without creating a misconception, for "venous return" is used in a different sense in America. The book is concerned with the anatomy, physiology, and pathology of that part of the circulation, including the blood depots, which lies between the venules and the tricuspid valves. The veins form the principal part of the system; they are conceived of as reacting as a unit to physiologic and pharmacologic agents, as having control of the amount of blood in the depots, and as being a chief factor in the distribution of blood between the various parts of the circulation. The relationship of this system to the commoner conditions of disease is the main subject of this book.

The authors' most interesting contribution to the subject has been secured by means of a new clinical test to demonstrate the presence or absence of an excess of blood in the "circulation de retour." With the subject in the horizontal position, the pressure is recorded with a manometer which is connected to a needle in a vein near the elbow. The legs are then passively elevated at an angle of 60° for fifteen seconds, and then lowered to the horizontal for fifteen seconds; following this, the right upper quadrant of the abdomen is compressed with both hands for fifteen

seconds. The venous pressure is measured at fifteen-second intervals. In normal subjects, these maneuvers do not affect the venous pressure; if they elevate it, the test is positive.

From their own observations, and from estimations of venous pressure, blood volume, blood velocity, and cardiac output which they have gathered largely from the literature, together with the clinical manifestations, the authors attempt to draw a picture of what is happening in the circulation in each of the commoner diseases, with emphasis on the role of the veins and depot organs. The examples which follow are chosen from those which are most novel to Americans.

Congestion in heart failure is believed to be a manifestation of increased blood volume. It is of two types, namely, hypervolemia with high venous pressure, and hypervolemia with relatively low venous pressure. The difference between them is attributed to the degree of venous constriction, which may be a compensatory reaction to support a weakened heart, but also, under certain conditions, may cause further cardiac embarrassment.

In addition to arterial hypertension caused by arteriolar constriction, the authors speculate about another form which is primarily the result of venous constriction; by increasing cardiac filling, this would increase cardiac output, thus raising blood pressure against normal arteriolar resistance.

Lack of tone of the venous walls, in addition to many other factors, is believed to play a large part in shock and collapse.

These and the other theories which are discussed are put forward modestly as working hypotheses only. The multiplicity of factors involved and the difficulty of evaluating them are repeatedly emphasized by the authors.

It is not hard to criticize the book. The chapter on treatment is the most unsatisfactory part. The American school is far more critical of therapeutics than the French, and, in the absence of any evidence whatsoever, will hesitate to admit the value of a large number of drugs, baths, and other agents which, in addition to standard remedies, are said to benefit patients, sometimes by acting on the veins. One wishes that more factual data had been given, and that the relation between the facts and some of the theories had been set forth more clearly. Although many authors are mentioned by name, the reader who is concerned with the facts is handicapped by a complete lack of specific references. There is no bibliography in the book.

This monograph makes a serious attempt to improve our conceptions of diseases of the circulation. The old theories which endeavored to explain all the phenomena of circulatory disease in terms of heart and arterioles are certainly outmoded, so that this presentation is timely and stimulating. It is difficult to say how successful the authors have been, for they are working in a field in which it is hard to secure convincing evidence, either for or against their views, but the same criticism could be made about many current theories concerning the heart and circulation which students of the subject are sometimes inclined to accept, more because they are familiar than because they can be supported by convincing evidence. Therefore, this monograph should be read by all who are interested in cardiovascular theories; it will stimulate some hard, and much needed, thinking.

All Americans will join in the hope that the vicissitudes of war have not interrupted the authors' work.

ISAAC STARR.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

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